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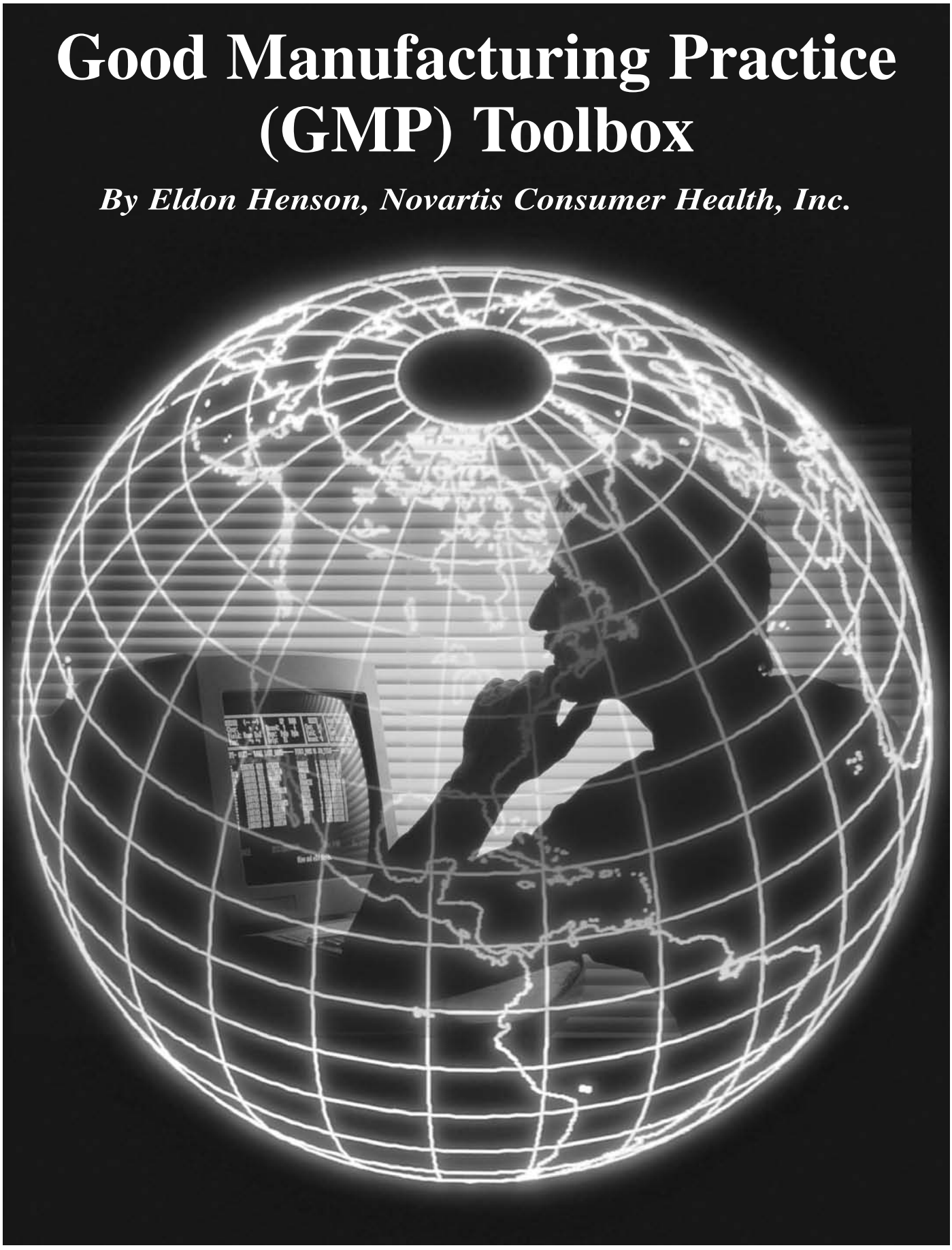

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By Eldon Henson, Novartis Consumer Health, Inc.

T A B L E O F C O N T E N T S

Introduction to the Good Manufacturing Practice (GMP) Toolbox

…there are certain basic requirements of GMP regulations that can help management understand the "whys" and "whats" of compliance.

by
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Introduction to the GMP Toolbox

HELPING MANAGEMENT UNDERSTAND THE REQUIREMENTS OF GMP

The concepts and requirements of Good Manufacturing Practice (GMP) are often difficult to understand, even for professionals in industries regulated by the Food and Drug Administration (FDA). So, for upper management to have the level of understanding necessary to balance the need for compliance with the requirement to "hit the numbers," is a challenge we often face. Certainly, managers of pharmaceutical and medical device companies that have entered into consent decrees with FDA, and paid fines above $500 million, understand how compliance can affect profitability. However, there are certain basic requirements of GMP regulations that can help management understand the "whys" and "whats" of compliance. A brief description of some of these basic requirements follows.

21 CFR 210 and 211 – The Law

The first key concept for management regarding GMPs is that these requirements are the Law, not merely recommendations or guidelines. There is a tendency among those not experienced in FDA-industry to feel that GMPs merely describe "best practice" or desired systems. For example, International Organization for Standardization (ISO) 9000 requirements do not have the same status of "the law" in the U.S. as do requirements listed in the Code of Federal Regulations (CFR). Because 21 CFR 210 and 211 have legal status, the U.S. Justice Department has extensive powers to ensure compliance. For example, product in the marketplace can be seized, fines can be levied, and personal liability can be assigned. So, management must understand that GMP must be taken seriously, and the requirements listed are just that – requirements.

21 CFR210 and 211 – Minimum Requirements

As FDA regulations go, the content of 21 CFR 210 and 211 are relatively few pages. The document we call GMP is not all-inclusive. The following statement is included in 21 CFR 210.1:

> *"The regulations set forth in this part and Parts 211 through 226 of this chapter contain the minimum current good manufacturing practice methods…"*

So, when these current regulations were written (originally issued about 1963, major revision in 1978, and revised in 1988), it was contemplated that changes in technology and standard practice would occur. Thus, we cannot use the excuse for non-compliance the comment that "it doesn't say we have to do that." The following are some examples of "current" requirements that are not specifically mentioned in 21 CFR 210 or 211:

- Internal auditing – there is no specifically mentioned requirement for an internal audit program: however, this is clearly an FDA expectation
- Process validation – clearly a current expectation, though not mentioned
- Cleaning validation – standard expectation now of FDA investigators

There are many other examples of changes in pharmaceutical technology that were not contemplated by the authors of GMP over 25 years ago. Thus, this "minimum requirements" comment assures that pharmaceutical practice will modernize as technological advances occur.

GMP Changes – So, We Must Improve

If the GMP regulations published in 1978 have not been substantially revised since then, how do the requirements remain modern, and what does FDA use as the standard for GMP? There are really several ways that GMP remains "current:"

■ Publications of Guidelines and Other Reference Materials by the FDA

FDA has routinely, since the original pharmaceutical GMP was implemented, published industry guidance documents. These guidelines cover a variety of topics, and are intended to aid FDA investigators during inspections. However, industry uses these Guidelines extensively to modify, improve, and upgrade GMP compliance. For example, prior to the 1980's, little information was available regarding compliance to GMP cleaning requirements, other than develop and follow an adequate cleaning procedure. In 1988, after the occurrence of cross-contamination of the finished drug product, Cholestyramine Resin USP with agricultural pesticide residues, FDA formalized cleaning requirements, including cleaning validation, by publishing the *Guide to Inspections of Validation of Cleaning Processes* in 1993. Though this guide did not represent "new' requirements, it did clarify and specify FDA expectations that are standard practice today.

■ Implementation of New CFR "Parts"

A fairly recent example of changing GMP requirements is evident by the publication and implementation in 1997 of 21 CFR Part 11: Electronic Records; Electronic Signatures. When new technology becomes available and in wide use, the need for FDA to expand expectations occurs. This is the case with electronic records and electronic signatures. Though FDA provided guidance on computer system validation previously, the technological advances outpaced specific guidance to the point that new requirements were necessary. Rather than provide a "Guide" to formalize expectations, such as was done with cleaning validation, the area of electronic records and signatures required new requirements. Because these requirements are "new," the use of either a modified 21 CFR Part 211 was required, or an entirely new 21 CFR Part 11.

■ Public and Written Comments and Opinions by FDA

A third mechanism for keeping GMP "current" is the use by industry of public oral and written comments and opinions offered by FDA representatives. Whether or not intended by FDA, public comments made at public meetings can often result in changes in compliance strategy. Two examples:

- FDA's *Human GMP Notes*[1] are often quoted and used by industry to either establish FDA expectations, or provide final guidance on issues. For instance, until the *Human GMP Notes* indicated that no data to justify a bulk hold of 30 days for solid products would generally be expected, various opinions existed regarding the need to generate data to justify even short hold times. This communication by FDA established the "current" GMP requirement that remains today.
- Requirements for Computer System Validation (CSV) were communicated publicly long before the FDA issued written guidance. This public forum allowed firms a head start on FDA expectations without waiting either for publication of the Guideline or FDA enforcement actions.

■ Legal Actions

The Barr Decision of 1992[2] is the best example of how legal actions can impact "current" Good Manufacturing Practice (cGMP) requirements. Though some concerns had been expressed before the de-

cision regarding the handling of laboratory Out-Of-Specification (OOS) results and blend homogeneity and sampling, the final decision of Judge Wolin changed significantly the way industry addresses these topics. Thus, the GMP requirements changed with the decision of a judge, not legislators or FDA in this example.

■ FDA Regulatory Actions and Expectations

Perhaps the most used mechanism for keeping the "c" in cGMPs is the specific regulatory actions taken by FDA. In this day of information, obtaining specific FD-483 observations issued to other companies is routine. Warning Letters can be obtained directly from the FDA web site. So, there are few "secrets" in the pharmaceutical industry today. Most firms regularly review these documents to monitor inspectional trends. When it appears that the FDA has cited one firm for an issue, the responsible action is to internally review operations to assure that the same observation would not occur in your operation. When a new topic arises, even without learning all the details behind the observation, many firms will implement corrective action. Thus, the compliance hurdle continues to rise as a result of this "leap-frog" approach to staying ahead of the FDA. This practice does have some negatives because it is possible to react to the events at another firm needlessly.

FDA also increases regulatory demands through this process. When an investigator finds a highly advanced system or control process at one firm, it becomes easier to find fault or deficiencies in other firms. Consciously or not, this highly advanced system now becomes the yardstick with which other firms are compared. An example of this higher expectation is the use of Installation Qualification (IQ), Operational Qualification (OQ), and Performance Qualification (PQ) protocols to qualify and validate equipment and systems. These protocols are not required by 21 CFR 210 and 211. However, these protocols became "industry standard" because they represented an excellent system for compiling qualification requirements. Today, FDA expects well-established and broadly used IQ/OQ/PQ protocols for equipment qualification.

The End Does Not Justify the Means

Another basic GMP requirement not well understood by some is that the end does not justify the means. This is best understood by examining the exact wording of 21 CFR 210.1(b):

> *"The failure to comply with any regulation set forth in this part and in Parts 211 through 226 of this chapter in the manufacturing, processing, packing, or holding of a drug shall render such drug to be adulterated…"*

It is not enough that finished pharmaceutical products meet all specifications and other requirements. Unless they were manufactured in accordance with GMP, drug products can be deemed adulterated, and be subject to regulatory action. Adulterated means that product is unacceptable, and cannot be commercialized. Some examples of actions prohibited as a result of this requirement include the following:

- Manufacturing operators experience problems with a batch during tablet compression. So, though specific requirements for press speed and compression force are listed in the batch record, they modify the process outside these ranges to achieve acceptable tablets. Though the tablets meet all physical and chemical specifications, they were not manufactured using required manufacturing parameters. Thus, they may be considered adulterated if marketed.
- Many pharmaceutical products must meet United Stated Pharmacopeia (USP) requirements. The USP specifies tests and limits for many product attributes. During testing of a USP product, the Quality Control (QC) analyst determines that a new instrument can be used to more quickly and with greater accuracy provide an assay result. So, the analyst modifies the USP method to use the new method without proper change control and approval. Despite the fact that the results obtained are likely correct values, product released using this method may be considered adulterated because unapproved methods were used for testing.

Current GMP mandates that all requirements be fulfilled, not merely those specifications that might define analytical or physical acceptability of the product.

Management is Responsible

Another requirement very clearly specified in GMP is the fact that management is responsible for fulfilling these requirements. The wording in 21 CFR 210.1(b) is clear:

> *"…the person who is responsible for the failure to comply, shall be subject to regulatory action."*

Management cannot claim ignorance of GMP regulations, or the compliance status of the firm. 21 CFR 211.180(f) requires:

> *"Procedures shall be established to assure that the responsible officials of the firm… are notified in writing of any investigations conducted… any recalls, reports of inspectional observations issued by FDA, or any regulatory actions relating to GMPs brought by the FDA."*

So, it is essential to understand this and assure that management understands.

There are several actions that can be taken by FDA and the U.S. Justice Department to assure management responsibility for GMP compliance:

- Imprisonment: There are examples of pharmaceutical officials that have been imprisoned because of violations of GMP requirements. It should be pointed out that most of these cases involved flagrant violation. However, this is not always the case.
- Fines: FDA has more recently utilized personal fines for those involved in GMP violations. These fines can be extensive.
- Debarment: Another action more routinely taken by FDA is to debar individuals involved in GMP violations, including management. Debarment involves disallowing affected individuals from performing GMP-related duties in any capacity. Individuals debarred are listed in the *Federal Register*, and firms must verify that no debarred individuals are functioning in prohibited duties when applying for new drug approvals.

These actions and personal responsibility should motivate management to know both GMP requirements, and the current status of compliance activities in the firm.

GMP Requires an Adequate Quality Unit

A key theme of GMP is the requirement for a Quality Unit (QU), and overall QU oversight of GMP activities. In the U.S. meat industry, it is common that a representative of the United States Department of Agriculture (USDA) have residence in the plant. This USDA representative provides ongoing guidance on regulatory compliance, conducts routine inspections for sanitation, and provides government approval that meat shipped meets all quality requirements. In much the same way, the authors of GMP have delegated this oversight role to the QU. This unit is intended to provide ongoing assurance that products are manufactured and tested by GMP procedures.

FDA does not really care what this QU is named. Most firms call this unit the Quality Assurance (QA) group. Several key elements are required:

- The QU must be adequate to perform its duties. This usually means that a sufficient number of qualified QU personnel be available to meet all regulatory compliance requirements.
- The QU must have independence. This usually means that the QU must have a reporting relationship separate from the production unit.
- The QU must have adequate authority to fulfill its duties. This usually means that decisions for release/rejection of materials or product be a QU function, and that others with a vested interest cannot overturn QU decisions.

GMP lists numerous specific QU responsibilities. These duties are shown in *Figure 1*.

FDA has been very aggressive in recent years to "reestablish" the authority and responsibility for GMP compliance to the QU. Most Warning Letters these days include statements indicating failures of the QU. Some recent examples include:

- "The procedures and control used by your Quality Unit are inadequate to assure the identity, quality, strength, and purity of your _____ product." – issued March, 2002.
- "Failure to have a Quality Control Unit (QCU) adequate to perform its functions and responsibilities as demonstrated by the number and types of inspectional observations." – issued August, 2000, and March, 2001, to two different firms.
- "Failure to have a QCU adequate to perform its functions and responsibilities, as required by 21 CFR 211.22." – issued January, 2001.
- "The Quality Unit failed to monitor and report unknown impurities in _____ tablets, USP." – issued April, 2001.
- The Quality Unit allowed batches of various products to be manufactured with potential metal contamination…" – issued April, 2001 to the same firm as above.

Figure 1

21 CFR 210 and CFR 211 Requirements for the Quality Unit

GMP Reference	Responsibility	Comments
21 CFR 211.22 (a) 21 CFR 211.84 (a) 21 CFR 211.110 (c)	Approval of materials*	• Responsibility and authority for approval (release) or rejection of all components, packaging, labeling, in-process materials, and finished products
21 CFR 211.22 (a)	Review and approve product records*	• Assure that production records are accurate
21 CFR 211.22 (a) 21 CFR 211.192	Investigations*	• Assure that errors and deviations are fully investigated • Investigate unexplained discrepancies or batch failures • Document all investigations
21 CFR 211.22 (a)	Contract manufacturing*	• Assure that contractors meet GMP requirements • Approve products manufactured, processed, packed, or held by contractors
21 CFR 211.22 (b) 21 CFR 211.165 (d)	Laboratories and testing*	• Oversight responsibilities for all testing and material disposition • Assure that all materials meet specification • Apply appropriate statistical criteria to release decisions
21 CFR 211.22 (c) 21 CFR 211.100 (a)	Approval of procedures and specifications*	• Responsibility and authority for approval or rejection of all procedures and specifications
21 CFR 211.160 (a)	Change control*	• Review and approve changes to production proce dures, testing procedures, specifications, standards, sampling plans, etc.
21 CFR 211.170	Retention samples	• Retain samples of all active raw material lots and all finished product lots
21 CFR 211.166 21 CFR 211.194 (e)	Stability program	• Establish stability intervals for all products • Maintain all stability records
21 CFR 211.180	Record retention	• Retain all records associated with production, testing, and distribution
21 CFR 211.180 (e)	Annual product reviews	• Annually conduct a review of all batches produced – all production, testing, complaint, recall, rework, investigation data – to determine the need for changes
21 CFR 211.192	Batch record review*	• Review and approve all records associated with batch production, packaging, and labeling
21 CFR 211.198	Product complaints*	• Review all product complaints • Investigate product failures • Document complaints and investigation
Many sections of 21 CFR 211	Auditing*	• Assure that written procedures are followed
21 CFR 211.220 (Proposed changes)	Validation*	• Review and approval of all validation protocols • Determine when changes necessitate revalidation

** GMP specifically state this to be a responsibility of the Quality Unit (QU) – other listed responsibilities are inferred to be, and usually are, quality unit responsibilities*

In summary, you cannot overestimate the importance placed by FDA on responsibilities of the QU. Management and individuals in the QU must reassert authority to assure GMP compliance, regardless of past practice or current company philosophy. In fact, the revised inspection technique of FDA called the Quality System Inspection Program (QSIP) includes a mandatory review of a company's quality systems.

Keeping Management's Interest in GMP Compliance

The process of keeping GMP compliance near the top priority for management is not always easy. The following are 10 suggestions that can help retain the visibility needed:

❶ Create a "FDA Compliance Manual" in which you include copies of 21 CFR 210 and 211,

key guidance documents, highlighted copies of Warning Letter citations, and detailed information on FDA actions, and fines relating to non-compliance. Distribute this to all members of site or top management.

❷ Meet with management on a regular basis to review the current status of compliance in your firm, plus new regulatory developments.

❸ Communicate the results of all internal GMP compliance audits, along with implications, action plans, and target dates.

❹ Develop a lunch hour seminar series on specific GMP topics, and invite management representatives to attend and participate, by providing one discussion on the importance of compliance to the company's bottom line.

❺ Include management team members on the circulation list for key industry news on FDA compliance issues.

❻ Assure that one or more key members of management participate directly in an FDA inspection.

❼ During FDA inspections, provide a daily download to management, and include detailed notes on each day's activities.

❽ Review GMP requirements for the QU (see *Figure 1*) with management, and discuss in detail the activities required to fulfill each responsibility.

❾ Schedule a half-day session with a key member of top management to tour key QU functions, review required batch documentation, examine and see the complexity of validation documentation, etc., to gain first-hand awareness of GMP compliance activities.

❿ Create a "Top Five" compliance vulnerability list that highlights the top compliance concerns, what they are, why they are important, and the likely outcome if remediation does not occur. Regularly update and communicate this list.

THE GMP TOOLBOX AND ITS IMPORTANCE

The GMP Toolbox is a representation of the essential tools for equipping an operation with solid and sustainable compliance to GMP requirements. A detailed discussion of the key tools included in the GMP Toolbox is presented later. However, a brief introduction to the GMP Toolbox, and the various types of tools are as follows. The GMP Toolbox is comprised of four basic types of tools:

❶ *Basic Tools*

Every good toolbox is equipped with certain basic tools. These basic tools are essential for nearly any project. These tools might include a hammer, screwdriver, wrench, and saw. No decent toolbox would exist without each of these. These tools are essential for the elementary tasks of construction. They are used to make the houses we live in, the furniture we eat from, and many elements surrounding us constantly. In the same way, the basic tools used to build GMP compliance are the tools that make all other activities functional and necessary. These tools are similar to the building foundation. Unless it is strong and unmovable, all construction upon it will be shaky and unstable. The basic tools in the GMP Toolbox include:

- Documentation Systems
- Training
- Validation, and
- Change Control

If these basic tools are present, well-established, and used with precision and control, the likelihood is high that the entire operation will operate efficiently and well within GMP compliance.

❷ *Assessment and Improvement Tools – Looking at the Past*

The second type of tool in the GMP Toolbox is assessment and improvement, or evaluating what has occurred in the past. For the carpenter, assessment and improvement tools could include a ruler, square, and level. For the pharmaceutical industry, these activities are critical in knowing how you are performing, and how operations can be improved. The assessment and improvement tools include:

- Complaint Systems
- Investigations, and
- Annual Product Reviews (APRs)

The best pharmaceutical companies routinely utilize inputs from these systems to identify opportunities for improvement, and continually upgrade compliance.

❸ *Prevention Tools – Looking at the Present and Future*

The third type of tool in the GMP Toolbox is the group of tools used for prevention. As you might guess, prevention of product problems and compli-

ance issues is the desired routine mode of operation. For the carpenter, the file or plane might be called prevention or correction tools. In the pharmaceutical industry, these tools include:

- Auditing
- Incoming Material Systems
- Supplier Qualification

By anticipating issues and problems by looking at current performance and future potential for issues, you can often avoid the trauma of regulatory concerns or material outages.

❹ *Material Release Tools*

Finally, the procedures, processes, and practices used for material release, and the disposition of problem situations – The Material Release Tools – represent the pinnacle of GMP compliance. The activities surrounding the generation and integrity of laboratory data, and the ultimate release of materials, often determine the difference between product quality issues or regulatory concerns, and a record and reputation for GMP excellence. Just as the master carpenter can see and feel his work when completed, and determine whether the work is good or not, so can those of us in the pharmaceutical industry determine the quality of our work. We can see daily the result of our labors, and feel a sense of pride in the lives we save or improve.

The remainder of this document will focus on the tools included in the GMP Toolbox, and offer practical suggestions on specific requirements and methods to achieve GMP excellence. Please note that due to excellent recent discussions and information on the tools of incoming materials and supplier qualification[3] and annual product reviews,[4] little discussion on these topics will occur in the GMP Toolbox.

Basic Tools of the GMP Toolbox

DOCUMENT CONTROL SYSTEMS

Why is Controlling GMP Documentation Such a Key GMP Tool?

An effective system for controlling GMP documentation is perhaps the most important tool in the GMP Toolbox. Without proper document control, there is little to no chance for the proper operational control demanded by GMP.

Most GMP-compliant document control systems include at least the following 12 elements. Instilling these elements as standard activities defines the concept of "QA Control." Each element is discussed in some detail below. In addition, an example Standard Operating Procedure (SOP) is attached that might serve as a model for establishing a proper GMP document control system.

Elements of "QA Control" for Documents

1. Definition of what documents are controlled
2. Unique number for each document
3. Specified format
4. Version control
5. Effectivity dating system
6. QA approval
7. Accessibility of documents to users
8. Control of access – print control
9. Change control system
10. Systems for archiving, storage, and security
11. Part 11 compliance for electronic records
12. Discipline: Use, control, change, storage, and availability

Definition of What Documents are Controlled

The starting point to establishing a "QA Controlled" document system is to define exactly what documents will be controlled. In the absence of this list, there will be routine questions regarding whether certain documents must comply with GMP requirements or not. For example, unless it is clearly defined that Preventative Maintenance (PM) procedures must have QA oversight, approval, and control, there may be a campaign by the Maintenance or Engineering organization to define these as having no direct GMP impact. Thus, there would be no need for QA review of changes, no need to establish proper version control, etc.

The list of documents under QA control can become extremely long unless some specific definition is established. One place to draw this line is to state:

> *"Any document or procedure that supports a direct GMP requirement or any document that could be presented to FDA during an inspection must be QA controlled."*

This definition casts a net that includes: SOPs, specifications, methods, forms, protocols, validation documents, stability protocols, calibration procedures, PM procedures, Master Batch Records (MBRs), and other related documents.

> ❂ ***HOT TIP!***
>
> *When establishing a document control system, focus on those most critical GMP documents first. Do not attempt to control all GMP-related documents all at once. Select those most critical documents, such as SOPs, specifications, methods, forms, MBRs, and forms, and control those initially. Then, expand document control as processes become more refined to include other GMP-related documents.*

Numbering systems

Proper control of documents requires that a numbering system exist that identifies each document as unique. There is no perfect numbering scheme. Some prefer a well-defined system that includes the ability to identify primary areas of use. Others prefer a system that utilizes a random or chronological numbering system. One numbering scheme that appears to be common and works well is the following:

• QCS – 001 – 00

In this system, the first two letters identify the primary department involved. For example, a list of departments could be set-up as shown in *Figure 2*.

Figure 2

Example of List of Primary Involved Departments

Department Identifier	Department Name
EN	Engineering
GP	General Plant
QA	Quality Assurance
QC	Quality Control
MR	Maintenance and Repair
SP	Solids Production

This list could be as extensive and detailed as necessary.

The third digit would identify the type of document. This is illustrated in *Figure 3*.

Again, this list would be as long as needed to include all document types you control.

The next three digits would simply be a chronological number. The first document of each type would be 001, etc.

The last two digits would be the version number. The initial version would be 00. The first revision would be 01, etc.

Figure 3

Example of Third Digit Identification

Department Identifier	Department Name
C	Calibration
F	Form
M	Method
P	Policy
S	Specification
X	Cleaning

Thus, this simple scheme results in a number that has some identification in it, plus is short enough to remember. In the example above, the document QCS-001-00 would be a QC specification, the first one issued, and the original approved document.

Format

To assure proper and consistent documents, it is important to develop a standard format that all documents will follow. The format should specify the specific section requirements for documents, including style, appearance, and content. It is important that there be consistency across all departments, and all types of documents.

There are several reasons why a standard format is important for procedures:

- A standard format gives the appearance of control and consistency – this is especially important to external auditors and FDA
- A standard format reduces the time for an employee to acclimate to new procedural requirements when moving from one department to another
- A standard format requires less time to read, understand, and find specific requirements than if each area had different procedural formats
- A standard format facilitates standard templates that can reduce time for changes and developing new procedures – a productivity gain

See the SOP example, starting on page 82, for more specifics on document format and how to "legislate" it.

Version Control

Of critical importance in document control systems is the mechanism for assuring that documents represent the correct version. For example, it should

be readily apparent when reviewing a document which version it represents. Each time a document changes, even to correct a typographical error, the version should move up. In the approach described in the attached SOP example, the version moves from 00 to 01 when the first change is implemented. The next change will result in version 02, etc.

> ❂ ***HOT TIP!***
>
> *When you reference QA controlled documents in other procedures, you should include, as the reference number, only the first six digits of the number. You should not include the version number digits. In this manner, you still clearly identify the document referenced, but you will not have to revise each document when the version number changes. For example, if you used all digits, including the version number, you would have to revise every document that includes this reference number each time a version number changes.*

Effectivity Dating System

Another key consideration is establishing the date on which any document becomes effective. For example, does the document become effective on the date of final approval, or when issued by QA, or after training occurs? This needs to be established and defined.

In most cases, the effectivity date is the date on which compliance to a procedure is required. Two approaches are common:

❶ After final signatures/approval, the document control group will establish an effective date that is two or three weeks into the future. During this period, any training or communication required must occur. Then, the document is issued on that date.

❷ In this approach, no effectivity date is assigned until all training and communication has occurred. When documentation is received that all requirements have been met, an effectivity date is assigned, and the document is issued.

The approach taken for effectivity dating really depends upon how documents are administered. If all documents are on-line (i.e., no or few paper copies), issuance can occur rapidly after all training is completed. Thus, approach number two may be more effective. If document issuance requires significant effort to replace paper versions of documents, or, if multiple sites are affected, approach number one may be more appropriate.

QA Approval

GMP requires that the QU review and approve all documents and procedures that could impact product quality. Thus, any document defined as QA controlled, must include QA approval. QA review and approval should be the final step in the document approval process prior to issuance of the document.

Accessibility of Documents to Users

It is not enough to establish good, clear, and well-document procedures if they are not accessible to users. One mistake often made is to control documents to such a stringent degree that access to users is limited. This inhibits the user from routinely referencing needed documents. It is a reasonable GMP expectation that any document needed in an area performing GMP functions should be readily available.

The typical means for allowing document accessibility are hard paper copy and electronic versions. Each has advantages and disadvantages. Paper copies must be controlled to assure that older versions are not used. Electronic copies are often difficult to use unless the monitor on which they are read is in close proximity to the work stations where activities actually occur. Whichever system is used, the users must have the ability to retrieve, read, and use needed documents.

Control of Access – Print Control

One difficult and often controversial topic regarding document access and control is the question of whether copying of paper procedures or printing of electronic copies is allowed. The issue is how to balance the need for control with the need for document access. Several approaches have been successfully used:

■ Prohibit any Printing or Copying Except by Designated QA Personnel

This approach causes more anguish by users, but greater control. The question always becomes, "How do I assure user access if printing or copying is prohibited?" Many firms that have adopted this approach find that after several months, users finally develop means to use controlled or official copies, or electronic versions of documents without the need for in-hand copies. Some copying may always be required. However, by establishing a sys-

tem whereby the designated QA individuals can provide and mark (with a stamp or other means) the document to clearly identify it as non-controlled, these concerns can be alleviated:

■ Allow Liberal Printing Relying Upon Disciplined Use of Controlled Copies

Some firms have successfully allowed very liberal use of copies of controlled documents. The ability to use liberal printing is dependent upon other systems in place to assure that obsolete versions are not used for GMP purposes. In some cases, liberal printing creates an environment in which employees are less likely to keep obsolete versions in desk drawers and other hidden locations. By making it easy to obtain a copy of a current document, the employee feels less the need to take a risk regarding obsolescence. However, most firms do feel that some controls on printing or copying controlled documents are necessary.

■ Controlled Printing

Most firms have taken a middle-road regarding copying or printing of controlled documents. Copying/printing may be allowed, but the uncontrolled copy is clearly marked to identify it as uncontrolled. For paper systems, the official copy usually includes a color stamp or mark to identify it as "official." When copied (using black and white copiers), the color is not maintained. Thus, only controlled copies have the color mark. For electronic systems, it is often possible to include an expiration date, date printed, or watermark (clearly visible text across each printed copy) to mark the print as unofficial. In either case, it becomes clear to auditors and users that a document is currently controlled or uncontrolled.

> ❂ ***HOT TIP!***
>
> *The use of a watermark for controlling document usage, and allowing ready access, also requires a system to assure that these uncontrolled copies are not used for GMP purposes. One approach requires that these uncontrolled copies be destroyed at the end of each day. Otherwise, there is the potential that an uncontrolled (and, thus, an obsolete version) will be used – a GMP violation.*

Change Control System

Change control is such a key element in pharmaceutical operations that it is a distinct basic GMP tool (see Section on change control). However, there are some specific requirements for document control systems:

- Changes to documents cannot occur in a vacuum. Document changes must include consideration of other activities that could be impacted by the change. For example, a seemingly simple change to a cleaning procedure can have broad impact. This change might impact cleaning validation, employee training, and have an impact on other similar systems or equipment. So, any document change must also consider the more global picture, and whether other systems must be evaluated.
- A change history record or log included with the document can be beneficial. Some firms choose to include a change history record, or log with all procedures (such as SOPs). This log can be beneficial in identifying the progression of a document from original to current, and highlight past practice to aid in investigations or quality improvement evaluations. See the Document Control SOP model for an example starting on page 82.
- Coordination of changes must be carefully orchestrated. Many document changes have broader impact than the modification of one document to a new version. In some cases, a change to one document can impact several others in a "domino effect." In these cases, several documents may have to be issued in a single day. These situations must be identified early, and be carefully coordinated to assure that one new version of a document does not create a conflict with another.

Other aspects of change control apply also to document systems.

Archiving, Storage, and Security

Other important elements in document control include the facets of archiving, storage, and document security. Documents that must be secured include:

- Master Batch Records (MBRs)
- Original SOPs and related source documents
- Completed batch records and other documents to support production
- Laboratory data
- Validation documents
- Specifications and methods, and
- Other key documents supporting GMP compliance activities

Proper storage or archiving is more than providing a filing cabinet to place documents. Documents must be organized to allow easy and sure access. In addition, document storage must be secure. Filing cabinets must be locked and area access limited. Did you realize that the completed batch record for batch of product not yet released could actually represent $250,000, or the value of the batch of product? If the entire batch record was lost, and critical data could not be reconstructed, the batch may not be releasable. So, you should think of critical records in terms of value to the company.

Most firms also assure record archiving in a controlled environment. This environment should prevent moisture damage and, ideally, be halon-protected to prevent destruction in the event of a fire or related disaster. Records associated with GMP compliance should be considered equivalent to other intellectual property that must be protected to assure future catastrophic events.

> ❂ ***HOT TIP!***
>
> *One unique system for archiving critical GMP documents is a high-density carousel unit. These units, costing approximately $25,000/unit provide security, yet require relatively little floor space. Some systems have computer-controlled access that limits individuals to only those documents for which they have been approved or cleared.*

Part 11 Compliance for Electronic Records

All activities relating to document control systems must consider the need for compliance to 21 CFR Part 11 requirements. As you probably know, Part 11 requires specific precautions and controls for electronic records, including:

- Audit trails for document generation
- Verification and operational checks
- System, password, and electronic signature security
- Documentation controls
- Special controls and requirements

Any GMP-compliant document system using electronic records and/or electronic signatures must comply with Part 11. This regulation has been law since 1997, so excuses regarding this being a "new requirement" probably no longer are legitimate.

Pharmaceutical Discipline

The key word in any document control system is "discipline." Discipline is that culture of compliance or adherence to requirements… the commitment to do what is right and proper… the unwillingness to compromise those limits and requirements specified by internal documents or GMP. Discipline in a pharmaceutical operation means that employees will adhere to procedures or requirements even when science or expediency may dictate an alternate action. Discipline is an essential requirement in pharmaceutical operations. This attitude and culture are critical to document control as well. By establishing clear requirements for documents, documentation, and document control, then enforcing these requirements, you will have the greatest opportunity to cultivate the level of compliance required.

Basic Tools of the GMP Toolbox

TRAINING

How Can All GMP Training Requirements be Met or Exceeded?

A typical FDA inspection will usually involve an evaluation of the training conducted at the site. During the inspection, the investigator will observe employees performing various activities and functions, and record the names of some, along with the tasks or activities observed. Later, the investigator will request documentation that each employee was trained in that activity. The investigator will expect that this training documentation includes training on all procedures impacting the activity and any other related documentation, such as general GMP training.

So, how can you be prepared for a review of the training function during an FDA inspection? There are essentially four activities that can help you prepare for that review:

❶ Understand GMP training requirements
❷ Establish a training program that includes the key types of GMP training required
❸ Establish a system for qualifying trainers, supervisors, and employees to perform key tasks and activities, and
❹ Document all aspects of the training program and individual training events

The following is additional information on each of these activities that may assist you in establishing or fine-tuning your own training program.

GMP Training Requirements

"Training must occur to enable persons to perform assigned functions."

Any individual involved in the manufacturing, processing, packaging, testing, movement, or distribution of drug or device products must have adequate training to perform assigned tasks. Many refer to this as On-the-Job Training (OJT). This means that, while a person assigned to a GMP-related task (such as operating a tablet press or liquid filler) must be trained to operate particular pieces of equipment, he or she must also have training on the plant environment, requirements for manufacturing the product, and the general operation of the facility.

FDA investigators expect workers to have the necessary training to operate equipment, handle documentation, conduct laboratory tests, supervise others, and properly conduct the tasks that they have been assigned to perform.

"Each person must have GMP training for the specific job performed."

This means that an employee operating a tablet press or liquid filler must also have adequate knowledge of their specific job function, such as how to prevent product contamination, how to document problems, and how to know if components are released. An employee must understand all of the GMP requirements associated with his or her job.

"GMP training must be performed by an individual qualified to train."

Trainers must have the training, education, and experience to make them "experts" in the field, or at least very knowledgeable about the subject. If the person assigned to conduct GMP training is not qualified, the depth and quality of the training is likely to be deficient. Bad habits can be transferred from one person to another in this way.

"GMP training must occur on a continuing basis."

GMP training must not be merely a one-time or annual event, but rather a day-to-day learning experience. GMP requirements must be reinforced daily. Employees must receive instruction when procedures change, when things go wrong, or when mistakes occur. GMP training is a daily activity.

"Training must be at sufficient frequency to allow employees to remain familiar with applicable GMPs."

All employees involved in GMP activities must have GMP training on a regular basis. This might also be called refresher training. The continuing GMP training mentioned earlier complements this "refresher" GMP training. The frequency with which you conduct refresher training depends upon your operation, its complexity, and whether changes or problems arise.

Types of GMP Training

• New Employee Training

New employees, who have never before worked in a GMP environment, typically need an initial orientation or training session. They must be introduced to what GMPs are, and what is expected of them.

• Ongoing and Refresher Training

This includes the day-to-day reinforcement of GMP, as well as regular GMP review sessions. Refresher training is necessary to assure that all employees have the necessary GMP knowledge, and to allow them to brush up on basic GMP requirements. Annual training may not be enough. Some firms have formal GMP training on a quarterly basis, or even more often, covering new topics each quarter. Refresher training is also a good time to cover and interpret new GMP regulations.

• Special Training

Training is often required for special reasons, such as when new processes, products, systems, or equipment are introduced. Under these circumstances, special GMP training sessions are necessary to keep employees informed.

• Training to Correct Problems

GMP training is sometimes needed to correct problems or address special concerns. This training may also occur following an audit that results in corrective action. The training might require a one-on-one session with an employee, or a larger group session with employees who have been affected by the problem. Employees need to understand what happened, and what is being done to prevent the problem from reoccurring. Often, employees will be asked to provide recommendations as to how similar problems can be prevented in the future.

• Training to Communicate New or Revised Procedures

Training is often required to update an employee on new or revised SOPs. Changes to SOPs may be common, and when they occur, training is needed to ensure that all employees will properly implement these changes. This training should occur prior to the implementation of the revised procedures.

Employee Qualification

Qualification means to certify or to declare that an individual, system, process, or equipment has been proven capable of performing a specific task. Qualification is required for employees and those who train them. 21 CFR 211.25 defines qualified as:

> *"…shall have education, training, and experience, or any combination thereof, to enable that person to perform the assigned functions."*

Employees are usually considered qualified if documentation is adequate to verify training in required topics or activities (see Documentation of Training). However, additional documentation is usually required to consider trainers and supervisors "qualified." One accepted approach for documenting trainer and supervisor qualification is to develop a Qualification Record. This Qualification Record is similar in many ways to Curriculum Vitae (CV) in that it summarizes key employee information. An example is illustrated in *Figure 4*. This Qualification Record fulfills the GMP requirement to consider all education, training, and experience, and includes a conclusion that this employee is qualified to train and supervise certain specific activities.

Documentation of Training

Documentation of training can occur in literally dozens of different ways. Some use paper systems, others use database systems, and still others use web-based systems. Each can work, and each has been shown to meet FDA expectations. All training documentation systems are designed to answer one simple question:

> *What documentation do you have that Jane Jones has been properly trained to operate that filler?*

It is also good to be able to answer the related question:

> *Can you show me documentation of all training that Jane Jones has obtained, when it occurred, and the content of training?*

To provide real-time, ready access to all of Jane Jones training can be a difficult activity unless an organized documentation system exists.

One approach that has proven effective, whether or not paper or database systems are used, is the checklist approach. An example is presented below for Jane Jones, a filler operator in a pharmaceutical company. The approach taken in this example is to develop a training checklist for each job title. In Jane's case, the checklist is developed for the title "Filler Operator." The specific tasks that might be performed by a Filler Operator are listed in the first column. In the second is the specific type of training or SOP reference. Jane has signed and dated at the time each training activity occurred, and the trainer has verified that this training occurred. Any comments related to this task could be recorded in the Comments column. Though a cumbersome approach, this checklist will serve to provide, in a single record, the training activities completed by Jane.

As you can see, the checklist approach is highly sensitive to the ability of Jane and her supervisors to hand-record each training event onto the record, and the integrity of the training information listed on the original record. This system does not allow easy access of SOP training, nor can one sort for specific information on others that received the same training. This is the reason most firms now use a database system. By using a simple relational database, you can more easily track training information and generate reports. The three concerns that still remain are:

❶ Setting up the database in a manner that makes data entry easy and accessible
❷ Maintaining signed original records of training to support electronic database entries
❸ Validation issues

Web-based training systems can solve some of the problems and issues relating to database management and validation. However, the concerns with ongoing costs and ease of establishing training entries must be considered, though overall costs may be less when the total training system costs are calculated.

One additional issue regarding training has arisen in recent years. How do you know that the GMP and OTJ training you conduct is effective? In

Figure 4

Qualification Record

Employee Name: John Doe Employee Number: 535629

Job Title: Supervisor, Solids Packaging Line

EDUCATION

- *High School graduate – Central H.S., St. Louis, MO*
- *Associate in Science degree – Meramac Community College, St. Louis, MO*

TRAINING

- *Supervising in a GMP Environment Course, in-house (May, 2001)*
- *Comprehensive GMP Training, 5 days in Miami, Florida (February, 2000)*
- *Basics of Granulation Science, 3 days in Cincinnati, Ohio (December, 1999)*
- *Packaging Engineering Conference, 4 days in Chicago, Illinois (June, 1999)*
- *Comprehensive Electronics, 2 days in Newark, NJ (October, 1998)*
- *Many other general training activities (see complete training file)*

EXPERIENCE

- *2 years – Supervisor, Solids Packaging operations at Acme Pharmaceuticals, Inc.*
- *5 years – Operator, Solids Production department at Acme Pharmaceuticals, Inc.*
- *11 years – Mechanic (general manufacturing areas) at Omega Pharmaceuticals, Inc.*

Based on this employee's education, training, and experience, he/she is qualified to **TRAIN** employees in the following:

- *All activities relating to the Solids Packaging Line*

Based on this employee's education, training, and experience, he/she is qualified to **SUPERVISE** employees or operations relating to the following:

- *All activities relating to the Solids Packaging Line*

Department Head Approval: _____ Date: _____

Quality Assurance Approval: _____ Date: _____

some cases, FDA investigators have made citations relating to this issue. Most firms now conduct some type of training evaluation in the form of a quiz at the end of training to verify and document effectiveness or comprehension. When conducted, these records should also be retained.

In short, to quote an unknown FDA representative, "If it isn't documented, it didn't happen." Thus, unless you can document that training occurred, you are likely to be cited for GMP deficiencies.[7]

VALIDATION

The Purpose of Validation

One of the most common questions for individuals new to the world of GMP is "What is validation, and why is it important?" Most of us have wondered about the answer to that question from time to time. The FDA defines validation as:

> *"Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes."*

The entirety of validation is proof – proof that a process will do what it is purported to do consistently. So, the answer to the question about validation should deal with the concept of proving that the process you describe is true and will work time after time. But, take a look at that question again – it also asks, "…and why is it important?" The answer to this part of the question deals with concepts, such as:

Figure 5

Training Documentation Record

Job Title: Filler Operator

Name: Jane Jones Employee Number: 467533 Employment Date: May 23, 1997

Activity	Training Type	Trainee Signature/Date	Trainer Signature/Date	Comments (Retraining, etc.)
General GMPs: • Initial • Annual • Annual • Annual • Annual • Annual	Classroom to cover applicable aspects of 21 CFR 210 and 211	J.Jones 5/23/97 J.Jones 4/13/98 J.Jones 5/5/99 J.Jones 2/24/00 J.Jones 6/13/01 J.Jones 4/4/02	S.Smith 5/23/97 S.Smith 4/13/98 B.Wilson 5/5/99 D.Gilmore 2/25/00 D.Gilmore 6/13/01 D.Gilmore 4/8/02	Retraining will occur annually.
Safety: • Intro • HazCom • LO/TO • Chemical • Electrical • Fire	Classroom to cover basic aspects of various safety topics	J.Jones 5/23/97 J.Jones 6/13/97 J.Jones 5/28/97 J.Jones 7/14/00 J.Jones 10/10/98 J.Jones 6/6/97	H.Hohmstadt 5/27/97 H.Holmstadt 6/16/97 J.Dean 5/30/97 H.Holmstadt 7/15/00 H.Holmstadt 10/22/00 J. Dean 6/6/97	See Safety Department files for updated training.
Line clearance – removing materials from previous production	FAL-001 FAL-002	J.Jones 6/2/97 J.Jones 6/2/97	W.Williamson 6/3/97 W.Wiliamson 6/3/97	
Filler cleaning	FAC-001	J.Jones 5/24/97	S.Smith 5/24/97	
Filler set-up	FAO-023	J.Jones 7/13/97	S.Smith 7/13/97	
Filler operation	FAO-022	J.Jones 7/15/97	S.Smith 7/15/97	Jane was qualified to operate the filler on 7/15/97. S.Smith 7/15/97
Bottle dumping	FAO-013	J.Jones 5/26/97	B.White 5/28/97	
Bottle descrambler cleaning	FAO-014	J.Jones 3/31/00	J.Jamison 3/31/00	
Bottle descrambler set-up	FAO-025	J.Jones 8/13/99	B.White 8/15/99	
Bottle descrambler operation	FAO-011	J.Jones 8/13/99	B.White 8/15/99	Jane was qualified to operate the descrambler on 8/15/99. B.White 8/15/99
Capper cleaning	FAO-101	J.Jones 9/23/99	D.Askew 9/26/99	
Capper set-up	FAO-104	J.Jones 12/12/99	D. Askew 12/12/99	
Capper operation	FAO-112	J.Jones 12/12/99	D. Askew 12/12/99	Jane was qualified to operate the capper on 12/12/99. D. Askew 12/12/99
Fill weight checks	QCW-155	J.Jones 7/15/97	J.Dean 7/16/97	
Cap torque testing	QCT-010	J.Jones 7/14/97	J.Dean 7/14/97	
Room monitoring	FAO-063	J.Jones 2/23/98	B.Green 2/25/98	
Room cleaning	FAC-002	J.Jones 5/25/97	B.Green 5/25/97	
Batch record documentation	QAD-214 FAD-003	J.Jones 5/25/97 J.Jones 6/25/97	E. Gomez 5/25/97 E. Gomez 6/25/97	
Fill weight investigation	See investigation 123-A42	J.Jones 2/23/01	C.Cusick 2/23/01	
Bottle defect investigation	See investigation 456-B42	J.Jones 4/4/02	A.Murphy 4/4/02	

Note: For training on latest version of SOPs, see SOP file.

- To fulfill GMP requirements
- To minimize product losses, rework, and investigations
- To provide consistency and predictability
- To avoid product recalls
- To protect our customers

Validation, at its root, is the process of proving validity. Is the process valid? Should we be using this process? Can we count on it? In the end, validation is merely the way we should run our business. We need to establish that what we do makes sense, is predictable, and will do what it should do.

Developing a Validation Program from Scratch

If you had never heard of the term validation, but wanted to prove the validity of your process, how would you do it? Let's look at a simple example process:

ABC tablets

Step 1. Weigh and add ingredients to blender

Step 2. Blend the ingredients for 20 minutes at 15 rpms

Step 3. Discharge the blend into a tote bin

Step 4. Compress the blend into tablets

Step 5. Package the tablets into bottles

Proving that this process will consistently produce a product meeting its specifications will involve several activities:

- Describe the process: Any validation activity must start with a detailed description of the process being studied. An adequate description of the process must also include a definition of the outcome of the process that is in our case, a product. We must assure that the product is defined by thorough specifications. For ABC tablets, the process could be described as listing the MBR process to be studied, equipment involved, and final product specifications to attain.
- Determine the critical parameters: The critical parameters are those factors that indicate at each step of the process whether the process is properly functioning, and will determine the ultimate outcome of the product. For ABC tablets, each step listed could be defined as a critical step. By indicating that these are critical steps, you must establish that the effectiveness and repeatability are acceptable for each step.
- Challenge the critical parameters: For each critical parameter, you must define the parameter ranges to be studied, tests to be performed, and acceptance criteria. Let's look at the blending step. In this case, the time and speed of the blender are definitely critical steps. Thus, you must assure that at 20 minutes of blending at 15 revolutions per minute, the resulting blend will be homogeneous. So, the challenge would involve blending three batches under required conditions, sampling at predetermined locations, and testing. Homogeneity must be defined in the test protocol, along with methods for sampling and testing samples.
- Report the results, reach a conclusion, and gain approval: After challenging the parameters, you must assemble the data into a report that summarizes the data, describes the outcome, and recommends a conclusion. This final report will be the ultimate proof that the process is valid or validated.
  The final report should state whether the process has achieved validation requirements, and if the process is considered validated. Any deviations or discrepancies must be explained, along with their impact on the study.

This example is an overly simplified one to illustrate that validation can become complex and involved, even with a simple, clear process. The main point with validation is to design a study that will withstand close scrutiny to answer the question, "Is the process valid?"

Basic Requirements for Validation

Before you are ready to begin the validation activities, you must have the necessary GMP infrastructure in place. This infrastructure is part of the process, and should be challenged, along with the process, and includes activities, such as training, calibration, establishment of preventative maintenance programs, etc. Every activity of the validation process must involve the use of a pre-approved protocol or document describing what will be evaluated, how it will be challenged, and the expected

outcome. A typical validation "package" will encompass all aspects of the process and equipment studies to meet the burden of proof.

Validating Equipment

Validation of equipment is essentially the collection of data to prove that the equipment is designed, installed, and operates properly. In most firms, this collection of data is in the form of protocols called IQ, OQ, and PQ. The sum of these efforts will work toward a final conclusion that the equipment is ready and able to perform to meet the desired result.

Process Validation

Process validation usually is the study or studies designed to prove that the process will produce conforming products consistently. The example above with ABC tablets is a very simple version of a process validation study. The end result is to, hopefully, reach the conclusion that the process is validated for producing ABC tablets.

Much has been written about process validation that will not be repeated here. It is noteworthy, though, that process validation continues to be a primary inspectional target for FDA, and poor process validation still results in product recalls each year.

Computer System Validation

Computers must be validated in much the same way as all other manufacturing equipment. To FDA, computer hardware is generally treated similarly to manufacturing equipment, and software is akin to documentation. So, the combination of hardware and software working together to fulfill a function must be challenged and tested to prove validity; the same as any other process.

Again, industry publications are full of current and informative material on the basics and advanced technological advances in this area (see **IVT**'s products and publications on Computer System Validation at www.ivthome.com).

Maintaining Validation

After a system or process has been validated, the work has not ended. The maintenance of validation is just as important as the initial validation. The change control system is a critical component of validation maintenance. Change control is the process of evaluating changes to assess the continued validity of a process.

Most firms also utilize the Annual Product Review (APR) to assess the need for revalidation. This review, plus any other inputs, investigations, or issues, may indicate the need for revalidation. Even when no revalidation is warranted "for cause," many firms require that revalidation reoccur on a scheduled basis, such as every three years. This routine revalidation assures that the sum of many small changes will not mask larger issues that could result in product or process failures.

CHANGE CONTROL SYSTEMS

What are the GMP requirements for change control?

Much has been written about change control, and how it can be implemented. In this section of the GMP Toolbox, the requirements of change control will be discussed. In other words, these are the "key, critical, basic" elements that every change control system must have:

- A written, established process for initiating changes
- System for tracking changes in process
- Initial review to assess scope of change
- Review and approval of change stakeholders
- Review and approval by QA
- Assessment for regulatory filing impact
- Implementation plan
- System for tracking open implementation plan items
- Final change close-out
- Communication systems

A Written, Established Process for Initiating Changes

As with most elements of GMP, the change control process must be predetermined and written. One key for change control is that the process should be as easy to follow as possible to assure compliance with the process. In other words, everyone should know how the process starts. Thus, everyone knows that to initiate any kind of change, there is one form, and one way to initiate the process.

The change control SOP should be descriptive, but a flow chart is often beneficial to aid understanding. By creating a simple step-by-step flow diagram, individuals not necessarily familiar with the change process can efficiently initiate a change.

One important consideration to remember about

change control is that unless the process is "user friendly," individuals may be tempted to implement changes outside of the formal change control system. By creating a process that is understood and easy to follow without time-consuming and cumbersome steps, you have a better chance to assure that all changes will be captured and properly evaluated before they are implemented.

> ❂ ***HOT TIP!***
>
> *In many pharmaceutical facilities, there are different change control systems for each of the major plant systems. For example, one change control system may exist for equipment, another for documents, and yet another for processes. To facilitate a culture in which everyone knows what to do and how to do it, consider implementing a universal change control system that is used for all systems. To initiate ANY change with this approach, there is a single form to complete that begins the process. In this way, everyone will be on the same page regarding the mechanism for initiating any kind of change.*

System for Tracking Changes in Process

Change control is easier to monitor and manage if each change is identified with a number to provide uniqueness. By assigning a sequential number, you can more easily track the status of each change.

Change control tracking systems can be simple or complex. The simple systems involve a spreadsheet that merely identifies the basics of the change (impacted area, description of the change, initiator, etc.), and the current status of the changes. More complex and comprehensive tracking systems use databases that tie changes together with other elements of the quality system (such as validation, document control, etc.). The choice of what level of complexity to use depends upon individual needs.

The important element of tracking systems is merely to provide a means to know what changes have been proposed and the status of each.

Initial Review to Assess Scope of Change

Early in the change process, a review is needed to assess the scope of the proposed change. A seemingly simple change can impact many systems. For example, a proposed change in packaging line speed may appear simple and innocuous. However, a line speed change can also impact other systems… equipment qualification, employee training, packaging system validation, operation SOPs, MBRs, line efficiency, preventive maintenance procedures, or frequencies, etc. Unless the overall impact of a proposed change is evaluated, the change can negatively impact other systems or areas.

Thus, it is important that an initial review occur to identify all of the impacts of a proposed change to assure that the implementation plan addresses ancillary changes that result. This initial review should include individuals knowledgeable in overall operations. A list of possible impacted areas is included. Any change should include a review to address the following:

- Is training required? If so, who?
- Is equipment, process, cleaning validation, or revalidation required?
- Will any other documents require changes? If so, which?
- Will operator procedures change?
- Will MBR changes be required?
- Will PM changes be required?
- Will calibration be required or be impacted?
- Will equipment, facility, or process drawings require updating?
- Is there an impact on product stability, or will stability studies be required?
- Will specifications change?
- Will analytical methods change?
- Will an IQ, OQ, or PQ be required?
- Is there an impact on computer system validation? Part 11 compliance?
- What testing will be required to assess the change?

Review and Approval of Change Stakeholders

Any proposed change must be reviewed and approved by major stakeholders. This approval assures:

- That other impacts are considered
- That proper support and prioritization to the change will be granted, and
- That proper communication occurs

> ❂ ***HOT TIP!***
>
> *If, during the change approval process, any one stakeholder makes additional changes, all other approvers must have the opportunity to review and accept/reject the additional changes. Unless this additional review occurs, several changes could be approved that impact others without proper review, and without assessing the overall impact on all operations.*

Review and Approval by QA

GMP requires that the QU approve all changes that might impact product safety, purity, quality, efficacy, and strength. Thus, a QA approval of all changes must occur prior to implementation.

Assessment for Regulatory Filing Impact

In addition to QA approval, an assessment of all changes should occur to determine the regulatory filing impact. For example, if a proposed change will require pre-approval by FDA, the overall implementation plan may require that additional supporting data be generated. Or, ancillary changes will have to be held until regulatory approval is received.

Implementation Plan

A plan to implement change is an often-lacking component of the change control process. Certainly, the individuals involved know intuitively what steps must occur, but when these steps are not itemized with responsible individuals and target dates for completion, key actions can fall between the cracks. Thus, it is recommended that the change control process include a requirement to create a list of all key actions needed to implement the change. For example, if other document changes are identified to fully implement a change, the implementation plan should list the documents affected, the individual that has ownership of the changes, and the dates targeted for completion. By formalizing the implementation plan, a greater likelihood exists that the change will not adversely impact the state of control desired.

System for Tracking Open Implementation Plan Items

Some implementation plan action items will linger after the actual change has been implemented. For instance, a change to all master batch tickets may actually take several months to complete because the change will be phased in as needed. For this reason, a system is needed to track these open items to assure that they are eventually closed. Any of several systems could be used. For example, a simple database could be created that retains open action items, and relates each to a target completion date, responsible individual, and change control number. A few simple reports from the database can serve as a "tickler" system to allow close oversight and follow-up.

Final Change Close-out

Once all open actions have been completed and the change fully implemented, the change must be closed. This should consist of a formal review by QA to document that all actions have been completed, and no further actions are required.

Communication Systems

Finally, all effective change control systems have a process by which key individuals and groups are notified of pending and completed changes. The communication process can be as simple as an e-mail note or a paper copy sent to representatives of key departments. Certainly, the change approval process should include an approval by groups closely impacted by changes. However, there are other groups that have a need for information related to potential changes. For example, a change in the line speed on a packaging line can have an impact on production planning and scheduling. By implementing a communication system that provides information on these changes, the potential for assuring that any possible impact is assessed, and needed actions taken, are greatly improved.

There are many other aspects of change control that can be included in the change control process. Each system must be customized to meet the needs of the specific business and manufacturing environment. However, by incorporating these "change control requirements," your chances for a successful change control process are greatly increased.

Assessment and Improvement Tools of the GMP Toolbox

USING PRODUCT COMPLAINTS TO EFFECT IMPROVEMENTS

GMP Requirements for Complaint Handling

Several requirements for complaint handling are specified in 21 CFR 211.198:

- Written procedures are required
- The quality unit must review all complaints that could involve product failure
- Adverse experience events must be reported to FDA
- A written record of each complaint must be maintained and available
- An investigation is required for product or specification failures, and
- Complaint reviews must be included in APRs (21 CFR 211.180 [e])

In short, complaints must be handled in much the same way as any other failure or deviation

within the pharmaceutical manufacturing operation (more detailed information on investigations is included in the next section). Complaints must be recorded, an investigation conducted, QA must be involved, and appropriate action taken.

Capturing Product Complaints

One of the difficulties for any complaint system is to assure that all complaints are recorded or captured within the formal system. Most firms have a toll-free phone number that customers or physicians can call. When a complaint is registered, the critical information is logged. However, other complaints can be made, yet not easily captured within the system. For example, occasionally a complaint is made to a salesperson that will phone or e-mail the situation to the manufacturing site for review. However, this complaint will not be sent to the "official" complaint system administrator for formal logging.

A good complaint handling system will include a broad net to capture even these out-of-system calls. Each individual that might encounter such a call should be aware of the complaint system, and know how to get the complaint formally registered.

Investigating Complaints

Complaints should be investigated with the same zeal and level of detail as manufacturing or OOS investigations. A complaint that implicates product failure has the same potential of indicating a manufacturing or product concern as a deviation occurring prior to product release. (See *Figure 6*.)

Figure 6

Product Deviation Concerns Prior to Product Release

A Complaint for…	Could be an Indicator of…
A missing tablet or shortfill	Sporadic manufacturing failure
Undesirable taste or odor	Microbiological issues
Poor efficacy ("the product didn't work...")	Formulation or stability failure
Foreign object ("metal sliver in product...")	Massive product contamination
Product is cloudy	Formulation breakdown
Broken tablets	Formulation, compression, or stability issues
Missing batch code or expiration date	Labeling or packaging failure

It is imperative that the complaint handling system requires that each complaint be reviewed, and a documented decision regarding the level and type of investigation made. GMP requires that the decision regarding whether or not an investigation will occur be documented, and the individual making this decision be identified. The key point regarding complaint documentation is that each complaint must be taken seriously, and used as an opportunity to assess potential negative impact on consumers, and as a potential opportunity for process improvement.

Trending and Assessment of Complaint Data

Another important element of a good complaint handling system is the ability to monitor complaint trends. Most FDA investigators expect that you will convert raw complaint data into charts or graphs to illustrate whether the number of complaints for a particular problem and product are increasing or decreasing. A trend showing that a specific type of complaint is increasing should be viewed as a signal to investigate and determine a cause, if possible. Demonstrating that you are monitoring complaint trends is an indicator of an overall quality system that seeks to understand and improve products and processes.

Typical FDA Inspection Review of Complaints

Complaint records are nearly always reviewed during FDA investigations. These records provide an excellent record of real and potential product issues, and are instructive as to the overall quality systems in place at the firm. The following is one typical list of ten questions posed by an FDA investigator:

❶ Can I see a report of all complaints you have received in the last year by product and strength by date?
❷ Can I see your internal investigations for any or each of these?
❸ Who decides when a complaint is investigated? (Note: See 21 CFR 211.198 [b][3] which states that the written record include the name of the individual responsible when a decision is made that an investigation was not necessary.)
❹ How do you assure that all complaints are logged into your formal system? Do you register calls to the sales force, or complaints brought to your attention by FDA, for example?
❺ What actions were taken as a result of this (or these) investigation(s)? What is the status of those action items?

❻ What impact on the validated status of your manufacturing process would be indicated by these complaints?
❼ Have you received medical complaints? Do these indicate that your product is unsafe? Why or why not?
❽ What trend are you finding for complaints on this product? Are complaint numbers decreasing?
❾ Could I review your SOP for handling complaints, and compare that with what you actually do?
❿ Can I see the training records for those making decisions regarding complaint investigations and follow-up actions?

The ability to capture, organize, properly investigate, trend, document, and close-out complaints is a key indicator of the comprehensiveness of your overall quality system.

> ✪ ***HOT TIP!***
> *One key element of your complaint handling system that FDA investigators will likely examine is the manner and consistency that you test or analyze complaint samples returned to the manufacturing site. Are there examples in which you conducted complete testing for one complaint, and then performed only a "paper review" of systems for a similar complaint? Be sure that your complaint SOP specifies, as much as possible, circumstances that you will perform analytical testing or no testing. If you pre-determine the types of complaints that require analysis, and those that do not, you are less likely to be inconsistent in handling these samples.*

Using Product Complaints to Achieve Improvement

Product complaint trends are an important element in an overall quality improvement system. The input of consumers will provide information that no internal monitoring system can. The actual experience of those using the product can indicate failures or potential failures that could not be anticipated, in some cases.

The authors of GMP understood the potential of complaint data by requiring that this information be included in the APR. By reviewing all product performance data (analytical data, complaints, investigations, product returns, etc.) in the review, you should have a complete picture of product performance. In short, product complaints should not be viewed as a nuisance, but as new learning that will aid efforts to "perfect" the product, process, and performance.

INVESTIGATIONS

Definitions of an Investigation and GMP Requirements

What is an investigation and what does GMP require?

An investigation can be defined as:

> *A formal, organized, and documented study conducted to identify the cause in order to correct and prevent deviations and unexplained events in the manufacturing or testing of pharmaceutical products.*

Notice the underlined key terms:

- Formal: an investigation must occur in a prescribed and planned manner, not occur randomly – an SOP describing the investigation approach is required
- Organized: an investigation must be organized, preferably following a specific predetermined pattern of data gathering and assessment
- Documented: as with all GMP activities, investigations must be documented, including the study rationale, data, decisions, actions, and follow-up
- Cause: an extensive effort must occur to determine the single root cause, when possible
- Correct and Prevent: the ultimate goal of an investigation is to correct the problem and prevent a recurrence

21CFR 211.192 requires that "any unexplained discrepancy…or the failure of a batch or any of its components to meet any of its specifications shall be thoroughly investigated…" Thus, it is important that systems exist to capture, investigate, and document all such discrepancies and failures.

What Must be Investigated?

Events that should lead to formal investigations can usually be placed into one of three categories below. See *Figure 7* for examples of each.

- Deviation From Requirements: A deviation from an established or published requirement requires that an investigation occur. The key to this or any investigation is to learn what happened, and what can prevent a recurrence.

Figure 7

Examples of Deviations or Failures Typically Requiring an Investigation

Deviation from Requirements	Failure to Achieve Required Results	Failure in Product, Process, Equipment, or Personnel
• Required drying temperature not maintained • SOP requirements could not be followed • Time limits for conducting stability tests were not met • Incorrect analytical method used • Room differential pressure below limits	• Product final assay specification not attained • In-process tablet hardness results not achieved • Stability test failure • Sterility failure • Blend homogeneity fails • Black specks in solution • Environmental monitoring results fail	• Weighing error • Failure to blend for required time • Failure to use the proper cleaning procedure • Excessive capping for compressed tablets • Documentation for required process steps was incomplete • Equipment failure causing extended line downtime • Equipment visually dirty after cleaning completed • Foreign tablet found on-line during packaging

- Failure to Achieve Required Results: Failure to obtain expected results should result in an investigation. The inability to achieve an expected result is a sign that some facet of the process is not operating normally. Thus, an investigation should be conducted to determine what is happening, and what can stop or prevent failures.
- Any Failure in Product, Process, Equipment, or Personnel**:** Any real or possible product, process, equipment, or personnel failure should result in an investigation. In many cases, though a product failure has not yet occurred, a solid investigation can prevent a future failure.

How to Conduct an Investigation – Key Elements

There are several key elements of any effective pharmaceutical product investigation. Each element is listed below:

- **Discovery/Problem Description**: The initial step in any investigation is the problem discovery and description. Systems and procedures must exist that allow early detection and communication of problems. It is not sufficient to rely upon final batch record review to detect deviations and unexplained events. A culture that encourages and allows operators, technicians, and associates to raise concerns and issues as they arise, is imperative to early detection and correction of problems.

Once a problem is discovered, it is important that all known details be described in as much detail as possible. It is often difficult or impossible to recall later some of these necessary details. For instance, it is too much to ask an operator a month after an event whether she remembers if the red or green hose was used for a specific batch hookup. As soon as possible after a problem is discovered, all pertinent details should be assembled and recorded to properly describe what occurred, what conditions were present, who was involved, what products were involved, and what factors may have led to the problem. The investigation system, SOP, or form must include a listing of the types and kinds of details that should be gathered and recorded early in the stages of an investigation.

- **Containment**: Another key early step in the investigation process is to contain or limit the problem. Unless containment occurs, the problem can extend beyond its original scope, or become more difficult to assess. For example, if an equipment malfunction occurs on-line during filling, early containment can assure that affected product is isolated to limit involvement to minimal pallets of product.

Proper containment usually involves the following actions:

- Stop – halt production, testing, or other actions that could extend the problem until it is properly described
- Establish limits – define the start and stop points of the problem, and
- Establish control – isolate affected product or processes

An essential element of containment is to properly establish the limits of the problem. In the example of

an equipment malfunction during filling, the start point of the problem is likely when the first documentation of problems occurred or before. Without better documentation or definition, the initial start point may have to be defined as the point of last equipment maintenance, qualification, or successful operation.

- **Corrective Action**: Once the problem is described and contained, the next step is to determine the immediate actions needed to correct the specific problem and restart operations. In other words, you must now answer the question, "What do I need to do to assure that product manufactured (or tested, etc.) after restart will not be affected by this same problem?"

Corrective action can be as simple as correcting the equipment problem, resanitizing the equipment, shifting to a new lot of material, or other similar actions. However, you must assure that the problem is sufficiently described and a likely cause identified (see below), or the problem may still extend to other products or batches.

- **Cause and Analysis**: Possibly the most important phase of an investigation is to thoroughly analyze the problem, and determine the likely "root cause." A root cause is that single action or event that created the problem or deviation studied. It is important to determine the root cause to provide a sense of confidence that once corrective and preventative action has occurred, the problem will not reoccur. When the potential exists that the problem could reoccur, or if you do not know the root cause of the incident, you cannot have confidence that the problem is solved. So, extensive effort is needed to identify the root cause.

There are several successfully used systems that identify root cause. Several commercially available systems exist, and other "classical" systems are in use. The basic approach for each of these systems is as follows:

- Use an organized or brainstorming activity to identify all of the possible causes or related factors that could have been associated with the problem. One approach is to list the typical headings – materials, equipment, personnel, or systems/process – then utilize all personnel in the meeting to identify potential causes relating to each heading.
- Once possible causes have been identified or listed, you must categorize each potential cause as:
  - Verified cause: The cause is known or very likely to be a root cause
  - Unknown: The potential cause may have played a role as a contributor to the problem or as the root cause
  - Not a cause: You have been able to discount the potential cause as playing any role in the problem
- After categorizing each potential cause, you must construct a means to test, verify, or assess the potential for the cause as playing a role in the problem. In some cases, a review of existing data may serve to verify that the potential cause was or was not a factor. In other cases, such as with analytical testing concerns, you may have to conduct testing to discount a potential cause.
- When you have completed the analysis of potential causes, you have only a few likely causes. Final assessment of these can usually result in identification of the likely root cause(s).

This approach to identifying the root cause should involve personnel from various groups to assure that all views and diverse thinking are included in the assessment.

- **Preventive Actions**: For any verified or unknown cause, the investigation must eventually include an action to eliminate that cause from contributing to future similar concerns. The investigation should include a listing of these causes, and specific actions with individuals responsible, and target dates for completion. By conducting a thorough identification of possible causes and eliminating these causes from future involvement, you have a high likelihood that recurring investigational issues will not occur or be significantly reduced.

Preventive actions must be both specific and definitive. In other words, preventive action must result in change in order to be effective. It is not usually adequate for preventive actions to involve only communication or notification.

Poor preventive action… "Operators were informed of this problem…"

Better preventive action… "All operators were retrained on SOP XYZ-123 with focus on proper equipment set-up, monitoring, and documentation. The supervisor will reverify that each is qualified within 30 days…"

The latter action is more likely to prevent a recurrence.

- **Conclusions/Product Disposition**: A final step in conducting an effective investigation is to recommend and document the final conclusions and disposition of all products, materials, or systems affected. It is critical to clearly state what will occur with segregated materials, why that action was taken, and the justification for this final disposition. Unless these decisions are clearly listed, the possibility for miscommunication or unintended actions exists.

- **Follow-up and Tracking**: Once an investigation is closed, a system is needed to track promised actions to assure that, they were implemented as promised and, they were effective in eliminating the cause. Investigations with open action items must be visible in a database or other tool to allow routine review. Failure to assure that investigation action items are complete is a GMP violation often cited on FD-483s.

> ***HOT TIP!***
>
> *You must assure that open investigation action items be routinely reviewed and closed. Depending upon the volume of investigations in your firm, it is not unlikely that several hundred open investigation action items can accumulate in only a few months. One means to document action item closeout is to implement an "Investigation Action Item Closeout Form." This can be a simple form that merely identifies the action item by investigation number, lists the promised action and actions taken, and includes the individual and date verifying the action. This form can then be used later as documentation of closeout.*

Use of Investigations for Improvement

- How can investigations be tools for improvement?

The proper use of failure investigations can be a critical quality improvement tool. Though auditing can identify deviations from GMP and procedural or systems issues, failures represent actual problems. Failures are reality, not speculation. Thus, they provide a real opportunity to dissect operations to determine points of stress or opportunities to improve.

The key to linking investigations with improvement is establishing solid preventive action to address potential or known problem causes. As you eliminate problem causes, you minimize the opportunity for a recurrence.

Reviewing investigation trends is another tool that can indicate improvement opportunities. For example, if 20 failures occurred during the last quarter that indicated poor training as the root cause, it likely reveals a weakness in the training program that should be addressed. So, by establishing a system to categorize investigation occurrences and their root causes, you can identify further systemic problems.

Prevention Tools

AUDITING

Importance of Auditing

Much has been written about the importance and benefits of a solid auditing program.[6] It is clear that auditing internal operations and external vendors is a GMP requirement and FDA expectation. A good auditing program can identify issues and concerns that, if corrected, can lead to quality compliance improvement. It can also directly prevent quality and compliance concerns by assuring that deviations are corrected before they progress.

"One Question Away" – The Level 5 Auditor

Have you ever hosted an audit in which you said, "Whew, the auditor was one question away from opening a real can of worms?" Most of us know the feeling of an auditor coming within one small question of finding significant issues.

A good auditor is a "Level 5" auditor. This means the auditor questions systems down to at least five levels. Let's look at these levels:

- Level 1: This first level of questions merely asks for a description of systems in place to address GMP requirements. This level is the most fundamental area, and relies heavily on the word of the audited party
- Level 2: This level usually involves asking to review a copy of the SOP or procedures in place that describe a system or operation. In most cases, the auditor will compare the oper-

ation described in Level 1 with the SOP provided for review in this level
- Level 3: The third level of auditing involves reviewing examples of the system under review. The auditor, at this point, is examining the real-life output of the system described in Level 1 and written in Level 2 (only a very good auditor routinely advances beyond this level)
- Level 4: In the fourth Level, the auditor is focusing on a problem or non-routine example of the system or activity under review. Now the auditor has focused in an area that likely will truly reveal how the system operates or is controlled
- Level 5: At this level, the auditor is verifying that the problem was properly handled, the system actually functions as required, and that those auxiliary systems close to the system reviewed are controlled and functioning

It is difficult to visualize the levels of auditing depth by merely reading the descriptions above. So, let's look at some real auditing examples, shown in *Figures 8* through *10*.

Figure 8

Audit of Laboratory Out-of-Specification Results Process

Level	Type of Questions or Areas Reviewed
1	Would you describe your system for handling OOS results?
2	Could I review your OOS SOP?
3	Could I see a list of all OOS investigations for this product covering the last six months?
4	In reviewing this OOS investigation for a failed content uniformity result, how did you reach the conclusion that the reason for the failure was an improper sample preparation step? What was your justification for excluding this failing result?
5	Because the cause of this OOS was attributed to poor sample preparation technique, can I see the documentation of retraining that will prevent a recurrence? Were all other analysts also trained? Can I see documentation of their training? Has this specific analyst been involved in any additional OOS investigations? Would you describe your analyst training program?

Can you see the progression in questioning from the auditor above? The questions have progressed from an overview of the OOS handling procedures to a specific example. Then, the details of an example are reviewed, leading to a more in-depth inquisition about the cause of the failure. Finally, you can begin the cycle over again with the question, "Would you describe your analyst training program?" We have progressed through all five levels on OOS investigations to a new topic and Level 1 question. An approach that drills deep into a subject, then moves to a related one is a sure sign of an experienced and accomplished auditor. *Figure 9* is a look at another example.

Figure 9

Audit of Production Equipment Cleaning

Level	Type of Questions or Areas Reviewed
1	Would you describe how you clean that blender?
2	Could I review your SOP for cleaning the blender?
3	Can I review the documentation of the cleaning that was performed just prior to production of lot 12345 of ABC tablets?
4	Do you ever have cleaning failures? Is the blender inspected before use? How often is re-cleaning required? Can I inspect the blender (or another "clean" equipment), and visually inspect it myself?
5	I noticed that your cleaning procedure requires very specific procedures for cleaning the blender blades and discharge valve. How can you follow the procedure as described when there is no effective way to visually inspect the underside of the blades or discharge valve? Did your cleaning validation include swabbing of these locations? Is there any special precaution when you change from Leukotabs, a highly toxic material to ABC tablets? Did the cleaning validation protocol study the exact version of the cleaning procedure you have provided? Any cleaning procedure changes since cleaning validation? Can you describe your general approach to cleaning validation?

Again, you can see the progression to Level 5 where the auditor is digging rather deeply into the details of the cleaning procedure, and the validation of that procedure, eventually leading to the new topic of cleaning validation.

The real assessment of GMP compliance is that assessment that occurs when Level 5 questions are asked. *Figure 10* is a final example.

Again, you can see the progression. The very best, most accomplished auditors quickly move into Level 5 questions, and challenge the proper func-

Figure 10

Audit of Sampling Procedures for Incoming Raw Material

Level	Type of Questions or Areas Reviewed
1	Would you describe your procedures for sampling incoming raw materials?
2	Could I review your SOP for raw material sampling?
3	May I review the sampling area, and observe the technician collecting samples?
4	Do you ever reject materials for foreign material contamination? May I see a list of all raw material rejections in the last year? Do you verify that all materials are from approved suppliers? May I review documentation from all raw material lots rejected? How do you assure that your sample for analytical testing is random and representative of the lot? Have you been trained on proper sampling techniques?
5	You had three material rejections in the last year for foreign materials. Your SOP does not include special handling precautions for the metal lids of containers, or for cleaning materials before sampling. Do you think any of these rejections could have occurred as a result of contamination here? How do you know that the materials you receive are actually from the approved manufacturing plant? Can you discern between the various plants of the supplier? Is it possible for material with a failing result to be released? What systems exist to assure that sample integrity is maintained? How are samples controlled in the QC lab? Can you describe what happens to samples after leaving the sampling area?

tion and quality impact of the system under review.

Auditing is a key prevention tool in the GMP Toolbox. When done correctly, and with the ultimate goal of improvement, auditing can yield progressive and sustainable improvement. To make the most of auditing, a progression to those tough questions – Level 5 questions – will provide the most significant opportunity for revealing issues that need resolution.

Product Release Systems and Key Considerations

DATA GENERATION AND INTEGRITY

Laboratory GMP

The importance of laboratory data from a GMP perspective can be summed up by the following paragraph.[7]

> *"Data reported from a GMP pharmaceutical chemistry laboratory must have integrity. Data integrity means that the entire body of information, personnel, equipment, procedures, and activities which comprise these data, must together, provide unqualified confidence that the correct results were obtained and reported using the required methods."*

Many of the activities common in GMP laboratories are designed to assure the integrity of data reported. After all, all decisions regarding product release and, thus, consumer use are based on these data.

Though GMP are commonly thought to deal primarily with manufacturing operations, nearly as much text in 21 CFR 210 and 211 is devoted to laboratory operations. The same general requirements listed for manufacturing are operable for the laboratory – training, equipment qualification, method validation, documentation, investigations, etc.

So, the first step in assuring data integrity in a GMP laboratory is to assure that all systems, procedures, practice, and personnel comply with GMP requirements.

Chemical Data

All chemical data are not created equal. The mere fact that an analytical chemical result is within the required specifications does not mean that additional scrutiny is unwarranted. Most pharmaceutical laboratories develop a series of tiers for specifications that guide actions. For example, the broadest limits are usually stability limits, followed by regulatory limits, or release limits, etc. (see *Figure 11*).

These limits are usually defined as follows:

- Trend: Recent historical results (maybe the mean of the last 10 batches) – an excursion

Figure 11

Example Ranges for Typical Limits for Drug Product Assay

Type of Limits	Lower Limits	Upper Limits
Trend	97%	103%
Laboratory Guideline	95%	105%
Release Specification	92%	108%
Regulatory Specification	90%	110%
Stability Specification	85%	115%

from this range usually involves further supervisory review, but no OOS investigation
- Laboratory Guideline: Results below or above this range usually require an OOS investigation, though product can still be released if within release specifications
- Release Specification: The limits at which product can be released
- Regulatory Specification: The limits specified by the New Drug Application (NDA)/New Animal Drug Application (NADA) submission or monograph that serves as the legal limit for product release. In many firms, the release and regulatory specifications are the same, though some firms choose to have both to allow some variability for method or process variation
- Stability Specification. The absolute limits that product must achieve throughout the shelf-life. An excursion from these limits may require a recall assessment

So, you can see that the initial point at which some laboratory concern is expressed is when the result is compared against the recent historical results for that specific product (the trend). An out-of-trend result can often indicate a process concern or excess method variability for that analysis. In either event, an early review of data can often prevent a larger problem later. Reviewing results against trend results is certainly aided by an advanced LIMS or similar system. However, simple control charts on which each data point by product is plotted can provide the same quick assessment of results against the trend.

HOT TIP!

A recall assessment is an organized, multidisciplinary review of a product nonconformance situation for marketed products that determines the need for a formal product recall. This assessment is an internal committee, and usually involves representatives from QA, Regulatory Affairs, Medical Marketing, Distribution, and upper management. This committee will evaluate available data to determine whether a recall is warranted, and any needed communication to FDA. The use of this type of committee assures that all perspectives of the situation are considered, and that all required and prudent actions are taken.

Physical Data

Data on physical attributes of products (hardness, viscosity, dissolution, weight, thickness, clarity, etc.) should be treated similarly to analytical data. That is, failure to meet specifications results in an OOS investigation. Product disposition should be based on the regulatory impact of the deviation (i.e., Is this a deviation from NDA requirements?) and GMP requirements (i.e., Will this deviation result in a negative effect on purity, efficacy, safety, etc.?).

One key bit of advice is noteworthy. Product specifications, especially for physical attributes, must be carefully constructed. Only those attributes that truly could impact product quality should be given status of a product release specification. Those attributes of less significance should have the status of "guidelines" or "monitor" limits. These should not impact the disposition of a single batch, but be limits that help define and monitor the state of control. For example, the only reason tablet thickness should be a specification (provided controls exist for tablet weight, friability, and dissolution) is if thickness could impact product packaging. For liquids, you must ask how important product color really is as specifications are developed. Is the acceptable color only within a small range, or could greater variation be tolerated?

Contract Laboratory Data

Some feel that a contract testing laboratory is a quick and easy solution to testing backlog or throughput issues. There are several key factors that must be considered:

- Required oversight: Despite the testing resources saved by using a contract laboratory, significant resources may still be required. For example, it is important to conduct initial and additional regular audits of contract laboratories to assure that proper methods are used, and data can be relied upon. In addition, resources are still required to collect and ship samples, discuss testing methods and protocols, review and summarize results, and resolve issues.
- Total cost: As oversight requirements rise, the total cost, in addition to actual testing costs, significantly adds to the overall impact of using a contract laboratory. Any decision to utilize a contract laboratory must assess all costs to provide a realistic picture.
- Filing status: The steps required to gain approval of a contract laboratory must be considered. For instance, in some cases, a preapproval submission to FDA is required. In

others, significant procedural and documentation changes are required.
- Integrity of data: As with any laboratory, you must be concerned with data integrity and trust. Can you trust the personnel and organization of the contract laboratory?
- GMP status: A concern that must be considered before contracting with any laboratory is the overall GMP status of the laboratory. Will the laboratory have GMP concerns that impact your products, results, or product approvals?
- Confidentiality: In some cases, laboratories test products from many companies. In rare cases, confidentiality could be a concern. Precautions must be taken to protect intellectual property.
- Ability to meet timelines: Even with contract laboratories, timelines and priorities may inhibit the ability to meet promise dates. This should be assessed prior to contracting with a laboratory.

There are several good reasons why a contract laboratory may make sense:

- The contract laboratory offers testing capabilities you do not have
- To conduct easy, routine tests allowing the focus of your laboratory to remain with more challenging testing
- To meet a temporary project need
- To provide flexibility

All positive and negative impacts should be considered before making commitments to move testing to contract laboratories.

> ❂ ***HOT TIP!***
>
> *Whether or not you routinely use a contract laboratory, it is a good practice to have one or more contract laboratories qualified and approved for use in the event of an emergency or unexpected project deadline. Because it can take several months to identify, audit, and qualify an alternate laboratory, much time can be saved if this is accomplished beforehand.*

Use of Certificates of Analysis

FDA investigators expect that any raw material used in pharmaceutical products be accompanied by a Certificate of Analysis (C of A), (or Certificate of Conformance or Guaranteed Analysis or similar document) that describes the material. A C of A fulfills several requirements:

- It serves as the supplier's guarantee that the material is authentic – that is, the material is what it is purported to be
- It provides a description of the grade or quality of the material – for example, conformance to USP requirements is usually listed
- It provides trustworthy data to describe the purity, assay, or other attributes of the material
- It provides certification of the manufacturer and manufacturing site – these are critical elements for many raw materials, especially Active Pharmaceutical Ingredients (APIs)
- It may provide additional data or information not required by your specifications
- It provides key data that, if the supplier laboratory has been certified or qualified, can circumvent the need for your laboratory to conduct all tests on all lots
- It provides the personal confirmation, usually by a signature of a responsible individual, from the supplier that the material is acceptable for use

Proper use and respect for the C of A can be critical in a successful raw material (or component) testing program. Ignoring or dismissing deviations or missing information in a C of A is inappropriate. Requiring adherence to requirements can protect your company from the financial impact of the loss of multiple batches, or a recall due to the use of unapproved or unacceptable materials.

Data Review and Approval

Final data review is a critical element in assuring the integrity of analytical laboratory data. This "technical review" is a key GMP requirement. This review consists of a technically competent individual reviewing all data and other information to assure that proper techniques were followed and correct conclusions were made.

There are three keys to a proper review and approval of laboratory data:

❶ The reviewer must be qualified – the individual that provides a technical review of data must be qualified by a combination of "education, training, and experience" and the fact that an individual is qualified must be documented

❷ All data, including raw data, must be available and reviewed by the reviewer – a proper technical review should include a detailed review of

the method used, and all results (including raw data, charts, spectra, reagent preparation records, calculations, etc.), and the final result, must be repeatable by calculation by the reviewer

❸ The technical reviewer must be provided the time and authority to conduct a thorough review, e.g., the technical review must not be a secondary activity performed between analyses. This activity must be taken seriously, and the reviewer must have authority to reject any data not appropriately derived, documented, or defendable

Data reported from the laboratory must be relied upon as correct. In most firms, the final reporting of results is similar to a batch release. In other words, the laboratory is staking its integrity and reputation on each result reported. The data can be considered correct, and any actions relating to batch release can occur with no further review of processes used to obtain the results.

Because the integrity of laboratory data is so critical, and the basis for all pharmaceutical product releases, any action by an individual that undermines this integrity must be treated seriously. It is the author's opinion that any reporting of results not actually conducted is grounds for removal from the QU immediately. Any individual that would intentionally report incorrect results, or tests not conducted must be considered untrustworthy, and should be disqualified from service. However, individual company rules and practices must be followed, and used to handle these cases.

> ✪ ***HOT TIP!***
>
> *There is a distinct difference between a technical review of data and a release review. A technical review is that final review of all raw data, worksheets, chromatograms, calculations, etc. associated with testing to assure data integrity prior to release of the data. The release review is the review that assures results meet specifications prior to release of the product. Each review should be well-defined in SOPs.*

RAW MATERIALS

GMP Requirements for Raw Material Release

• What does 21 CFR 211 require relating to raw material release?

There are several primary GMP requirements relating to raw material release:

- Written procedures must exist for all aspects of handling, sampling, testing, and approval (21 CFR 211.80 [a])
- Each lot must be identified with a unique lot number that is traceable to the supplier manufacturing lot number (21 CFR 211.80 [d])
- Materials must be quarantined before use and stored appropriately (21 CFR 211.80 [b] and 211.82 [b])
- Written sampling procedures and plans are required, samples should be statistically representative, precautions must be taken to prevent contamination during sampling, and samples must be appropriately labeled (21 CFR 211.84 [b and c])
- Testing must be per written plans and at least one specific identify test must be conducted (21 CFR 211.84 [d])
- Materials must meet appropriate written specifications to be released (21 CFR 211.84 [e])
- Retesting must occur if storage could adversely affect the material (21 CFR 211.87)

• What are FDA investigator expectations regarding raw material release?

A review of raw material handling, testing, and release is typical in FDA inspections, and is an element of the Quality Systems evaluation for system-based inspections. In addition, this review nearly always occurs in pre-approval inspections. Most investigators will identify several key raw materials used in specific lots of finished product. The investigator will then review the receipt, sampling, and testing documentation for these materials. In many cases, all seven requirements of GMP listed above will be reviewed for these materials.

FDA investigators will review the material specifications, methods identified for each, then review the analytical data supporting release of these materials. Having a clear trail leading from finished product back to raw material receipt is critical to an uneventful review of these activities.

> ✪ ***HOT TIP!***
>
> *To assure that the "quality unit" has proper authority to approve or reject raw materials, an FDA investigator will often closely scrutinize investigations relating to raw materials released. If evidence is found that a non-conforming lot of material was given additional review, additional testing, or other opportunities to pass specifications, it might indicate that the quality unit lacks*

the autonomy to make the final lot disposition. To avoid the appearance of impropriety, assure that all decisions to overturn an original failing result, or to conduct additional testing is without interference from those outside the quality unit with a vested interest in using the material.

• Is an expiration date required for raw materials?

Either an expiration data or retest date should be established for all raw materials. For many raw materials, especially API's, the manufacturer will typically establish, using stability studies, a specific expiration. For many excipients, no expiration date is established. The using firm must develop procedures and processes that define how long materials can be used, when they have exceeded useful age, and when retesting may extend the expiration. One typical approach to handle the three scenarios is as follows:

❶ Expiration date established by supplier.
Most firms use the expiration date assigned by the supplier on a material. However, some firms choose to limit this. For example, a firm can state in receiving procedures that the expiration is "the supplier's expiration date or two years, whichever is shorter." This approach assures that the supplier assessment is considered, but that extended storage will not adversely impact the material. It is rare that a pharmaceutical manufacturer will override the supplier expiration, unless the firm has conducted testing or stability testing to verify that no degradation has occurred.

❷ No supplier expiration date.
When no supplier expiration date has been established, most pharmaceutical firms place pre-determined limits or expiration dates on materials. For example, many firms have SOPs that state that the expiration (or retest date) for excipients is two or three years, and for APIs is one or two years. Systems are in place to identify materials with upcoming retest dates to allow retesting and re-release prior to exceeding that date. In this way, material acceptability is established on an ongoing basis prior to use.

❸ Material has exceeded the supplier or in-house expiration.
Usually, when a material has exceeded the supplier expiration date, it is with some risk that the expiration date is extended. With stability-indicating analytical tests, it is possible to justify an extension for some materials. Most firms limit use to within the expiration date of the supplier. When a material is still within the supplier expiration, but has exceeded in-house limits, retesting can often support an extension of the date.

In all cases, SOPs must exist to define the approach for using raw materials and defining practice for expiration dating and retesting.

Establishing Specifications

• What factors are important in establishing specifications?

It is important during developmental stages to develop meaningful specifications. In short, specifications should:

- Define the quality or "fitness for use" of the material
- Address process parameters for achieving finished product specifications
- Match the analytical abilities of the laboratory conducting the testing
- Match the process of, preferably, multiple manufacturers

In short, the specifications established must fit the product, process, and laboratory of the finished product manufacturer, and be consistently achievable by the supplier.

One error that some firms tend to make is to include tests and limits in specifications that do not play a role in defining the quality of the material or fitting process requirements. For example, unless a raw material, finished product, or manufacturing process is prone to microbiological contamination or concerns, why include microbiological tests and limits in the raw material specification? It might be appropriate to conduct microbiological testing on the initial few lots or on a monitoring basis, but the specifications should fit both the needs of the process and product.

Remember, it is always easier to add to specifications later than to eliminate tests.

• How can you establish tests and limits that are not release criteria, but that you can monitor?

It is possible to include some specification tests that are in-house tests, or that provide needed data for other development activities when you do not desire to have these tests and limits classified

as "specifications." Several approaches can be used to achieve this:

- You can establish two sets of specifications: one called Regulatory Specifications (the legal specifications filed with the submission) and another one called Release Specifications. This approach allows you to conduct additional or in-house tests, yet more easily eliminate or modify them because they are not included in the filed or legal definition of the product and process
- You can include tests on a single specification, but include as the limit the term "Monitor" or "No limits specified." This allows you to conduct tests and collect data without being tied to limitations on changes and unexpected results. This approach should have a defined time limit, after which you no longer need to gather these data, or you convert the "Monitor" or "No limits specified" tests to actual limits
- You can conduct additional testing under a separate protocol or other QA controlled and approved documents. This approach is best used when data collection will occur over a defined time period, not long-term

• How should you communicate specifications to suppliers?

It is imperative that suppliers know and understand the specifications used to accept or reject materials. The best approach is to include a copy of the specification in the supply agreement, then provide updated copies when changes occur. The supplier should agree on the specifications – including the tests, methods, and limits – and abide by the customer disposition. Unless this communication has occurred, issues and disputes regarding materials will invariably occur.

Analytical Issues

• Should OOS investigations for raw materials be different from those for finished product?

Typically, all OOS results should elicit the same level of investigation. With raw materials, the tendency might be to merely avoid the additional time and effort required to conduct an OOS investigation, and simply reject the material. However, the possibility of laboratory error makes it essential that an OOS investigation occur at least to the point of assuring that the OOS was not a result of laboratory error. Then, work can cease and a rejection processed.

• How do you handle situations in which your laboratory reports a failing result, and the supplier insists that their passing result is correct?

Discrepancies between customer and supplier laboratory results are not uncommon. Several actions can be taken to resolve these discrepancies:

- Conduct a thorough OOS investigation to assure no laboratory error occurred
- Contact the supplier and compare analytical methodology – often, differences in methodology can explain differences in results
- Each laboratory can conduct parallel testing using samples, if available, of the discrepant material and a fresh sample. This should identify if a bias does exist in one or the other laboratory, and it should identify if a potential sampling error occurred
- Evaluate the benefit from testing individual samples, not a composite, to profile the lot of material. This may help assess potential non-homogeneity in the lot
- If discrepancies or differences in opinion still exist, consider contracting with a contract laboratory for "referee" testing. This is usually an early request by the supplier, and one not welcomed by the pharmaceutical company customer
- Conduct a joint investigation with the supplier to determine the root cause, and identify an action plan to prevent a future occurrence
- Agree to disagree, and consult the supply agreement for resolution of the differences

As a pharmaceutical manufacturing customer of raw materials, I will almost never consider using referee laboratory results. From a GMP perspective, it is nearly impossible to defend overturning in-house failing results with those from a third-party laboratory. However, this step may be helpful in resolving which laboratory may yield biased results – an aid in the investigation.

Finally, when a disagreement over results does occur, you must recall that as a pharmaceutical manufacturing customer of raw materials, you have only two choices when these issues occur:

❶ Work with the supplier to satisfactorily resolve the issue, and alleviate future issues
❷ Source the materials from another supplier

If alternative two above is not possible, too costly, or would result in production delays, aiding the supplier in resolving the problem may be the better choice.

Physical Inspection Issues

• Is an OOS investigation required for failing physical inspection results?

Yes, some level of OOS investigation should occur for any failing result, including a failing physical inspection result. At a minimum, the possibility of an inspection error should be eliminated. In addition, you must recall that the reason for conducting a solid investigation is to identify the root cause, and implement permanent corrective or preventative action. In the case of failing physical inspection results, the ultimate goal of the investigation is to eliminate the source of the problem, even if this involves working closely with the vendor to implement corrections at the manufacturing operation.

• How rigid are specifications for description?

As you are probably aware, description is largely subjective. For instance, a common description for a raw material is "white, crystalline powder." So, would this description exclude material that is slightly off-white? Who defines off-white?

When developing specifications for description, it is important to incorporate as much objectivity as possible. For example, white can also be described in terms of standard color palette numbers. So, you might also describe white as "white, between 242 and 248 for xyz color standard."

• What level and types of foreign material contamination are tolerable?

Would material that meets the white, crystalline powder description fail if one or two miniscule black particles were observed in the sample? Again, some subjectivity is involved in this determination.

For foreign material, it is common that any foreign material in raw materials would be cause for rejection. Unless the identification of the material is known, and determined to have no impact on the product (i.e., scorched particles of the raw material), the default disposition should be rejected.

Documentation Issues

• Should a lot of material be rejected automatically if the C of A reports a result that fails your specifications?

Yes, any C of A result that would fail your specifications should result in lot rejection. Certainly, your in-house results may provide a passing result. However, the supplier failing result is similar to an OOS result, in that only a laboratory error would usually allow it to be overturned. One exception is the situation in which the supplier test method is different from your approved method. In this case, your in-house result would take precedence over the alternate method result of the supplier.

• How should you handle a mismatch between the C of A and material labeling?

Any mismatch between information on the supplier C of A and material labeling should be treated as extremely suspicious. This situation could signal counterfeit material, or a situation in which the material was actually from a manufacturing site or process other than that approved. This situation requires an investigation and written response from the supplier. Failure of the supplier to provide a satisfactory explanation or justification should result in material rejection.

PACKAGING COMPONENTS

GMP Requirements for Packaging Components

• What are the GMP requirements for packaging components?

GMP requirements found in 21 CFR 210 and 211 are similar for both raw materials and packaging components. There are essentially no differences in how materials must be received, handled, tested, and released. In addition, GMP requirements for retesting components after prolonged storage are also true for packaging components (see 21 CFR 211.87). Prolonged storage can impact the physical integrity of container/closure systems, and systems must be in place to assure that these components are acceptable at the time of use.

• What are typical FD-483 observations for packaging component deviations?

The following are several typical FD-483 observations for packaging components:

- The QU failed to implement and control systems, such that unapproved packaging components would be quarantined prior to use…
- Closures were not inspected or retested after extended storage. As a result, the tamper evident seals of some units warped and failed to function as designed when used…
- Excessive packaging component defects were observed during use. There was no investigation to determine the cause of these defects, nor the impact on this or related batches…

- The QU failed to follow the sampling specified for some lots of packaging components…
- The sampling plan in use for packaging components was not scientifically or technically justified as appropriate for the materials used.

These are only a few samples of possible inspectional observations. A key point is that depending upon the product manufactured, and criticality of container/closure systems to product quality, FDA investigators will carefully review sampling plans, specifications, methods of testing, and control systems relating to these materials. So, developing solid assessment and control systems, and following them is a key GMP element.

Physical Defects

• How should physical defects be classified?

Most firms develop a defect classification system based somewhat on the following:

- Critical defects: This defect would likely result in product failure or defect, or significant consumer complaints
- Major defects: This defect may, under appropriate circumstances, result in a product failure or defect
- Minor defects. This defect is an indicator of component manufacturing problems that could: 1) result in more significant defects or 2) result in cosmetic concerns or issues during use

Some firms have additional categories, such as Major A and Major B, depending upon needs. The acceptance plan used by most firms is based on military standards, or similar plans that specify a statistically-based number of samples to inspect and accept/reject levels, based on predetermined risk assessment. For example, if a critical defect could be deleterious to product quality, a very low risk for accepting a defective lot would be assigned. Likewise, the allowed number of minor defects is usually larger.

• If any critical defects are detected, should the lot be rejected?

The sampling and inspection plan that is developed and approved should be used. If the plan specifies that you Accept 0/Reject 1 critical defect, you should follow this plan.

• How do you handle situations when a defect could be either major or minor, depending upon who is reviewing it?

A mistake often made with packaging components is to attempt to customize acceptance criteria whenever a new defect arises, or leaves too much room for interpretation between defect classifications. For example, a defect occurs that is new. Some feel it should be a major defect, and others feel it should be a Minor defect. Who decides?

It is always best to have a defect classification system that anticipates all types of defects that could be encountered. However, this is rarely the case. In cases in which a conflict arises as to defect classification, a team assessment is usually the best way to arbitrate the concerns. But, the ultimate decision must be made by the QA function.

• Is it ever acceptable to release a lot of packaging components that fails incoming inspection?

A failing lot must be rejected unless a system exists to render the lot acceptable before use. One example of such a system is to allow 100 percent inspection for lots that fail incoming inspection, provided QA approves. This approach would be acceptable only for easily detected defects, such as poorly formed bottles, cracked caps, or illegible text. However, it is less effective for defects that must be measured, such as out-of-round and dimensional defects. The 100 percent alternative should be specified in the sampling/inspection SOP and systems to document the inspection to include number inspected, number of defects found, types of defects found, etc. must exist.

• What action is required if a critical defect is detected on-line after the lot has been released?

Most statistical sampling plans will virtually assure that no critical defect is present, provided the probability of the defect is equally distributed within the batch. However, there is the possibility that a critical defect will escape the incoming inspection. Often, this critical defect is detected on-line during usage. Depending upon the criticality of the defect, two choices are usually available:

❶ Stop using the defective lot and reject it
❷ Implement preventative actions, document the occurrence, and continue using the defective lot

The former approach is the conservative approach. The latter approach would require added precautions (such as on-line inspection) and added documentation. In many cases, no additional critical defects will be detected. In this case, the justifi-

cation for continuing to use the lot is that statistical probability would predict a low incidence, because the lot passed incoming inspection, and the added precautions taken would likely eliminate any additional defective units.

Inspection and Sorting to Resolve Issues

• Is it acceptable to 100 percent sort a lot of packaging components that fails initial incoming inspection?

In the author's opinion, it is possible to use 100 percent sorting to accept an incoming lot that fails routine statistical inspection. However, several precautions are required:

- SOPs in place must allow the 100 percent sort
- QA must approve the sorting process
- The sorting process must be proven or validated to render the lot acceptable (as defined by predetermined acceptance criteria)
- All actions are documented
- The vendor is notified and corrective/preventative actions are solicited
- The 100 percent sorting is not recommended for difficult-to-detect defects, and should only be used sparingly, not routinely.

• If sorting is allowed, should it occur prior to lot release, or can it occur on-line during use?

Depending upon the ease of which defective units can be detected and removed, the 100 percent sorting process could occur on-line. However, this process would violate the requirement that all components be inspected and released prior to use. So, the recommended approach is to sort off-line, re-inspect, and release/reject. If released, the lot of components can be used.

• Is inspection and sorting considered rework requiring QA approval?

Yes, any sorting or extended inspection to remove defective units should be considered rework or preprocessing that requires QA approval prior to the activities.

Documentation Issues

• Is an OOS investigation required for packaging component inspection failures?

Yes, an investigation is required, or at least strongly recommended for packaging component inspection failures. An investigation assures that the inspection process was properly conducted. In addition, an investigation should involve working with the vendor to assure that the root cause is identified and corrective actions implemented. A proper investigation is an important step in the quality improvement process.

• How should sorting and inspection results be documented?

If an OOS investigation is conducted for non-conforming lots of components, any sorting or inspection conducted to render the lot acceptable should be documented in the investigation. It is important to collect data on any other defects noted, their frequency, and, if possible, their location within the lot to better facilitate identification of the root cause.

FINISHED PRODUCT

General Systems for Batch Record Review

GMP requirements regarding batch record review and product release are clear and specific:

21 CFR Part 211.188

The section in 21 CFR Part 211.188 states:

> *"Batch production and control records shall be prepared for each batch of drug product produced and shall include complete information relating to the production and control of each batch." This section refers to the Master Batch Record, the approved batch record template that serves as the "official" procedure for manufacturing a product. This section also states: "These records shall include: …(b) Documentation that each significant step in the manufacturing, processing, packing or holding of the batch was accomplished…"*

21 CFR Part 211.194

Section 21 CFR 211.194 states:

> *"Laboratory records shall include complete data derived from all tests necessary to assure compliance with established specifications and standards..."*

21 CFR Part 211.192

The most important section located in 21 CFR 211.192 states:

> *"All drug product production and control records, including those for packaging and label-*

ing, shall be reviewed and approved by the quality control unit to determine compliance with all established, approved written procedures before a batch is released or distributed."

In general, all components of the batch record are assembled, records are reviewed, questions and issues are resolved, and the batch is released by QA. This review has several purposes:

- Assure compliance with all procedures: GMP regulations require that all written procedures for manufacturing and testing pharmaceutical products be followed. The batch record review assures that the required materials procedures are used in manufacturing product, and that all requirements for manufacturing and testing were met.
- Assure GMP compliance: GMP also require that any deviation from requirements be documented and investigated. Deviations could include problems in manufacturing, OOS results, or any other issue that could potentially impact product quality. One purpose of the batch record review is to determine if overall GMP requirements have been met.
- Assure product quality: The batch record review is also important to assure the quality of the product produced. It is essential to provide an independent review of all documentation and results to assure that requirements were achieved, and that the final product meets release specification.

One key element necessary to assure a complete and thorough batch record review is providing the reviewer with a means to know what should be present in the record. There are several approaches to this:

- Develop a batch record checklist: A product specific checklist that includes all required elements of the batch record can be an excellent tool for the record reviewer to assure that all components of the record are present. This checklist must be QA controlled and current. The use of this checklist also provides documentation that each element of the record was present and reviewed.
- Organize and number batch record pages: Some firms develop batch records to include all possible elements into the numbered batch record. Thus, assuring completeness involves only verifying that all pages are present. For example, if the record has 64 pages, each labeled with "page 32 of 64," etc., the reviewer needs only to assure that all pages are present to conclude that the record is complete. This is often not completely possible because batch records often include chart recordings, temperature strips, and other miscellaneous documents. The review must be aware of which of these are required to assure that the review is complete.

After all reviews of the record are complete and all problems/issues resolved, the batch can be released. In most firms, this process involves an entry into a computer system to modify the status of the batch in inventory. This critical step must comply with all computer security controls to assure that only the limited QA group personnel have the ability to modify product status to "released."

There are relatively few references available that provide specific guidance on how to handle real-life GMP issues relating to product release. Because it is difficult to organize and present this information in any other way, a series of questions and answers is presented to address some of the difficult questions encountered by GMP practitioners relating to the investigation, disposition, and release of pharmaceutical products. These questions and answers are organized into General, Solids Products, Nonsterile Liquids and Creams, Sterile Products, and Stability Results sections. It should also be noted that the comments and recommendations in these sections represent ONLY the opinion of the author and in no way should be construed as representative of the requirements of FDA, the opinion of the author's current or past employers, IVT, or any other entity.

Guidelines for Product Release

- What are the GMP requirements related to product release?

FDA investigators expect that every element of the batch record will be reviewed and approved by the "QU." In most firms, this function is performed by the QA group. So, the basic expectation of FDA (thus, GMP requirement) is that all data will be reviewed, any deviations from requirements documented, and that QA will verify that all GMP require-

ments have been met prior to product release.

- Must a batch be rejected if material from an unapproved vendor or unapproved manufacturing site was used?

Occasionally, systems in place fail to prevent material from an unapproved vendor from being used. Or, a supplier will change manufacturing site locations without notification to customers. These situations do not automatically mean that product must be rejected. If the material in question is the API, the answer becomes clearer. For the API, the only remedy is to quarantine the product and petition via normal procedures to approve the alternate vendor or alternate manufacturing site. This can mean pre-approval by FDA after accumulation of appropriate data (C of A results, stability results, etc.) for NDA/NADA products, or accumulation of appropriate data for non-NDA/NADA products. If the material is an excipient, some additional flexibility may exist (if the specific vendor or site is not filed in the NDA/NADA), but approval of the alternative and accumulation of required data is still required. The bottom line is this... you cannot merely approve the alternate material or site via treatment as a deviation. Additional data must be accumulated, and appropriate data assembled, to justify that the change has no adverse impact on the product.

- Can alternate methods be used, if scientifically justified, to support rejection of failing data?

In other words, if data from the approved method results in an inconclusive conclusion to an investigation, can alternate methods be employed to provide supporting evidence for overturning an OOS result? The answer to this is no. Alternate method data alone cannot be used to referee inconclusive results. Certainly, alternate methods can sometimes be useful in investigating an OOS result. However, merely reporting an alternate result is inadequate to justify reversal of a laboratory result.

- Can a batch be released with an overage of one percent for one excipient?

Minor weighing errors, delivery errors, or calculation errors can sometimes result in an overage for some raw materials. If the error is minor (minor must be defined), the error can usually be documented and investigated as a deviation. However, if the error is larger, it can be argued that the formulation is significantly altered. So, in these cases, you must document the error, and scientifically justify the impact on product quality and GMP compliance. Often, a batch with a minor overage that occurs inadvertently can be released if properly investigated and documented.

Solids Products

- Can a batch be released if blend uniformity fails and content uniformity passes?

No. A blend uniformity failure cannot usually result in batch release. If, during the investigation, there is evidence that sampling bias exists, the stratified testing approach defined in the Product Quality Research Institute's (PQRI) "The Use of Stratified Sampling of Blend and Dosage Units to Demonstrate Adequacy of Mix for Powder Blends"[8] may be considered. Using this approach, extensive testing of finished tablets can provide sufficient proof that a sampling bias exists. In these cases, the batch can ultimately be released based on extensive finished product results. However, finished product results alone are inadequate to overturn blend uniformity failures.

- Is it necessary to reject any batch with metal contamination?

The answer to this and so many GMP-related questions is "not necessarily." In the event of inadvertent metal contamination, if you can prove that the normal processes in use (i.e., metal detection and rejection systems) will eliminate the contamination, it may be possible to justify product release. In these cases, you must prove via validation data that the inspection system will remove with confidence the contamination.

You cannot rely, however, on metal detection systems to inspect quality into product with known metal contamination. Though validation data may exist, you cannot rely on metal detection to "clean-up" material with known contamination. For example, if you have product granulation (not yet compressed) that has some level of known metal contamination, you cannot determine to process the granulation with an expectation that the metal detection system will remove the contamination. This is a fine line. However, remember that metal detection systems are intended to remove that metal contamination that normally occurs as a result of product manufacturing. It should not be used as an inspection device to remove known, abnormal contamination.

- What process deviations should result in consideration to reject the batch?

Process deviations are departures from expected

parameters during product manufacturing. Some process deviations are minor (i.e., temperature spike to 38 degrees C when the in-process limits are 32º – 37ºC), and some major (i.e., departure from validated line speeds). All process deviations must be documented and investigated. However, relatively few automatically result in batch rejection. In general, process deviations that result in a significant departure from the validated process, or could impact product quality, safety, efficacy, or purity must place batch release in doubt. In some cases, process departures can result in successful rework, or they can lead to process revalidation to accommodate new ranges. However, the conservative approach for handling significant process deviations often results in batch rejection.

- What action is necessary if in-process physical results (i.e., tablet hardness) exceed guidelines?

FDA usually treats in-process guidelines as significant process limits. Thus, an in-process limit deviation should result in an investigation, and similar scrutiny that a process deviation might incur.

- Should excess tablet capping or breakage result in batch rejection?

Not necessarily. Though excess tablet capping or breakage for a single batch indicates an unexpected result that should be investigated, it does not necessitate batch rejection. The investigation team must assess the severity, frequency, and significance of this problem. The team may recommend release, rejection, or inspection/removal of deviant tablets based on this analysis.

- Should imprinting errors result in batch rejection?

Imprinting errors that result on product that could confuse a consumer or limit the ability to discern the specific unit of product, should be considered critical defects. The firm's sampling plan should designate the treatment of critical defects. A single unit that is illegible in an entire batch is not usually considered significant. However, a significant number of these critical defects would likely result in identification problems, and could result in a batch rejection or inspection disposition.

Non-Sterile Liquids and Creams

- What level of foreign material contamination should result in consideration to reject a batch?

Foreign material contamination of any product should focus on three key questions:

❶ Is the identification of the foreign material known?
❷ Is the foreign material a normal component of the product (i.e., undissolved raw materials) or inert?
❸ Is the level of contamination objectionable to consumers if proven harmless?

If you know for certain that the material is a normal product component or inert, the decision on disposition hinges on whether the foreign material is objectionable to a consumer. Thus, the keys to product disposition lie with material identification, then consumer acceptability.

- What actions should be taken when the bulk hold time is exceeded?

Exceeding the validated or guideline bulk hold time can result in product rejection. This decision is based on the risk associated with the deviation (i.e., is the product susceptible to microbiological contamination), and the ultimate scientific justification relating to the time extension. For example, how long beyond the hold time limit was the product held? Was it less than an hour, or was it three days? Have batches been rejected due to microbiological contamination? If so, would you expect this extension to be injurious to the product? Can you justify the extension based on history and results? Should you validate this extension?

All of these questions should be asked and considered by the investigation team as product disposition is considered.

Sterile Products

- Does a failed sterility result always result in batch rejection?

Yes, almost always. Only when you can prove that a sterility failure was the result of a laboratory failure, can you overturn a failing sterility result. Even when you believe you can attribute a sterility failure to laboratory error, there are regulatory risks to a release disposition.

Let's look at an example of one case in which a laboratory error can be definitive. If the microbiology laboratory utilizes control cultures with a unique biochemical profile, a sterility test finding in which this specific culture was the product isolate might be deemed laboratory contaminant. Thus, retesting may be justifiable in this case.

- What environmental monitoring failures should result in batch rejection, if any?

Typically, environmental monitoring is intended to monitor the state of control of the aseptic process, not necessarily to indicate if any specific batch is acceptable. So, if a sporadic environmental failure occurs for a batch, it would not necessarily indicate a concern with the batch filled that day. However, if environmental monitoring for a batch indicates multiple failures that could indict the cleaning process for the line, some doubt as to acceptability of the batch is indicated.

Environmental monitoring failures in which direct product contact sites are microbiologically contaminated should also render batch release in doubt. For instance, if post-filling monitoring of the filler nozzles indicates contamination with *Escherichia coli*, it may be difficult to reach a batch release disposition. In cases of environmental monitoring failures, the severity of the failure, and risk to the product must always be primary considerations regarding product disposition discussions.

• What action should be taken if the post-filling filter integrity test fails?

A post-filling sterilizing filter integrity failure will usually result in a batch rejection recommendation. In these cases, it is difficult to justify product release/sterility, even if sterility testing is acceptable.

Stability Batches

• Should all stability OOS results be investigated?

Yes, except those stability tests conducted to justify batch expiration extension. In other words, when a batch expired at 36 months, and results were obtained at 48 months, (in an effort to justify an extension), no investigation would likely be required, though certainly recommended, to verify no laboratory cause. This exception must be specified in SOPs. However, any other stability OOS should be formally investigated.

• What actions should be taken when a marketed batch has a stability failure?

A stability failure for a marketed batch should result in the following actions:

- ■ Initiate a formal investigation, including laboratory OOS investigation
- ■ If the result is confirmed, assess the impact on related batches – this should include testing of retained samples of similar products manufactured in the same timeframe
- ■ The initial goal is to determine if the failing result is a specific product or a process issue
- ■ At some point, but not at an extended time, a recall assessment should occur. This assessment must be documented
- ■ A decision regarding communication to FDA should be considered. In some cases, a Field Alert may be indicated
- ■ If the issue is product or process-related, some actions should occur (possibly revalidation) to correct/prevent the problem
- ■ The above actions should also include an assessment as to whether further production or distribution of released product should occur

A stability failure can be a significant event. Strong, decisive, and timely actions are necessary.

Pharmaceutical Elegance

Developing and Maintaining a Culture of "Pharmaceutical Elegance"

"Pharmaceutical elegance" can be defined as the total of all GMP and auxiliary activities necessary to achieve the following objectives:

- • Level of Compliance
- • Cultural Conformance
- • Self-Discipline
- • Attitude of Excellence
- • Personal Character
- • Commitment to Quality
- • Desire for Improvement

…necessary to meet and exceed GMP requirements and customer expectations relating to pharmaceutical products.

Let's look briefly at each of these elements of pharmaceutical elegance:

- • Level of Compliance: Certainly, GMP compliance is required for pharmaceutical elegance. However, compliance is more than words – it's a lifestyle. You need to reach the point that cutting a compliance corner is not even an option or consideration. You should achieve a level of compliance that allows you to state with absolute confidence that every employee, day or night, will always follow every procedure, document every activity, and comply with every requirement willingly and without hesitation. When employees willingly pick up a piece of trash in some else's department, or on the ground as they walk to the

parking lot, you will know that you are approaching that level of compliance needed.
- Cultural Conformance: In many firms, you can determine quickly whether the culture is one that promotes and achieves pharmaceutical elegance. Employees are neat, areas are clean, and everything is done with a sense of excellence. Pride in the products, work, fellow employees, and facilities is evident. In a culture such as this, where the little things are done well, you can be assured that the "big things" of GMP compliance will also be done well.
- Self-Discipline: GMP compliance requires significant self-discipline. Each employee must do the right thing, at the right time, and the right way all of the time. This becomes difficult during times of stress, pending deadlines, and customer demands. However, pharmaceutical elegance means that no temptation to cut a corner will be realized.
- Attitude of Excellence: A firm that achieves pharmaceutical elegance will be one that demands excellence of its employees, systems, and products. Excellence means to do more than is required, better than required, and faster than required.
- Personal Character: It has been said that character is what you do when no one else sees you. This is especially true in pharmaceutical manufacturing. If a firm has character, it will not bend under the pressure of shareholders, marketing, or upper management, and its individual employees are more likely to display character.
- Commitment to Quality: Everyone says they are committed to quality. Actions tell the real story. Are individuals encouraged to grow, to challenge the status quo, and to occasionally fail in order to improve? Are people held accountable and rewarded for the quality of products, systems, and processes? Can you see the improvement that has occurred in the past two years? Does the rumor of an FDA visit create fear and panic, or does it represent an opportunity to learn how to improve? These are signs that the firm is committed to quality.
- Desire for improvement: How can you be a firm with pharmaceutical elegance if you are not committed to and actively pursue improvement? The very nature of GMP is that quality improvement is elemental, an expectation, and codified in the law. Commitment also means more than words. It means that funding for personnel, facilities, and systems will be available to assure that the vision for future excellence is an everyday activity now.

- So, is your firm achieving or striving for pharmaceutical elegance?

Developing a Culture of Employee and Management Discipline

How does a large, well-known, and very successful pharmaceutical firm reach the point where they enter into a consent decree that involves $100 million in fines, new product approval delays, and extreme FDA oversight of operations, with ongoing fines and costs? Has the level of GMP compliance diminished to the point where FDA is forced to act? The reasons behind such FDA action are many – failure to take FDA actions seriously, lack of commitment to improve, inability to meet new GMP demands, etc. What actions can be taken to prevent such a chain of events from occurring in our firms? Is it really true that "it may happen to others, but it can't happen to us"?

Perhaps the two most critical words that can ensure that extreme FDA action will not be needed for our firms are *proactive enhancement*. By intentionally and proactively seeking ways and means to improve personnel performance, systems, and processes, we can best avoid the types of action taken in recent years by FDA. By staying abreast of the regulations, and anticipating future regulatory compliance needs, we can strategically plan for compliance improvement, not merely react to concerns noted by FDA.

Final GMP Toolbox Comments

Hopefully, it is understood that the GMP Toolbox, as presented here, is not the final authority on GMP, nor is it a comprehensive treatise on all aspects of GMP compliance. Its intent is to provide real-life, practical information on key aspects of GMP compliance to help the reader benefit from the author's experience. Though much of GMP compliance is black or white, there is much in various shades of gray. It is in these areas that the experience of others can help. ❑

About the Author

Eldon Henson is a member of the Editorial Advisory Board for the Journal of Validation Technology, *and a frequent contributor to* ***IVT*** *journals. He has written IVT's* Auditing Handbook, Quality Improvement

Handbook, Topic of the Day *Training Program for cGMPs, and numerous other articles on the topics of validation, documentation systems, annual product reviews, training, laboratory GMPs, and auditing. Henson is currently Director, Quality Services for the Novartis Consumer Health division based in Lincoln, Nebraska. He has previously worked at Boehringer Ingelheim, Sigma Aldrich Corporation, Abbott Laboratories, and Ralston Purina Company. He holds B.A. and M.A. degrees in Microbiology from Southern Illinois University in Carbondale, Illinois. Henson also has authored over 20 web-based GMP training modules for Eduneering (www.eduneering.com), based in Princeton, NJ. Henson can be reached at 402-327-8530, or by e-mail at eldonelaine@aol.com.*

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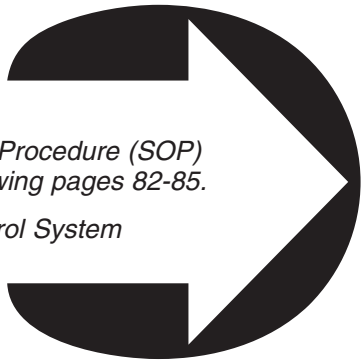

A Standard Operating Procedure (SOP) Continues on the following pages 82-85.

Titled: Document Control System

Article Acronym Listing

API:	Active Pharmaceutical Ingredient	OOS:	Out-Of-Specification
APR:	Annual Product Review	PM:	Preventative Maintenance
CFR:	Code of Federal Regulations	PQ:	Performance Qualification
cGMP:	Current Good Manufacturing Practice	PQRI:	Product Quality Research Institute
CofA:	Certificate of Analysis	QA:	Quality Assurance
CSV:	Computer System Validation	QC:	Quality Control
CV:	Curriculum Vitae	QCU:	Quality Control Unit
GMP:	Good Manufacturing Practice	QSIP:	Quality System Inspection Program
IQ:	Installation Qualification	QU:	Quality Unit
ISO:	International Organization for Standardization	SOP:	Standard Operating Procedure
		USFDA:	United States Food and Drug Administration
MBR:	Master Batch Record		
NADA:	New Animal Drug Application	USDA:	United States Department of Agriculture
NDA:	New Drug Application		
OJT:	On-the-Job Training	USP:	United States Pharmacopeia
OQ:	Operational Qualification		

Your Company's Name	**Standard Operating Procedure**	*Effective Date:* August 15, 2002
Document Number: QAP-001-01	*Title:* Document Control System	*Page:* 1 of 4

1. PURPOSE

1.1. This procedure provides instructions for the generation, use, and control of all GMP-related documents. Specific requirements for document change control are included in other documents.

2. SCOPE

2.1 This procedure applies to all documents relating to pharmaceutical products manufacturing, packaging, testing, or distribution at this site. This procedure applies only to the preparation and maintenance of Quality Assurance (QA)-controlled documents. Change control is covered in other documents.

3. RESPONSIBILITY

3.1. Document Author or Preparer – any individual trained in this procedure may serve as author for a document or change, however, any proposed document or change is subject to all review and approval activities described in this procedure

3.2. Document Approver – any individual qualified by training, experience, education, and the management of his/her area to comprehensively review a document, and render approval for content, format, and cGMP compliance

3.3. Quality Assurance (QA) – overall control of the document system, all activities relating to compliance with this procedure, and all cGMP requirements

4. DEFINITIONS

4.1. Effective date – the date a controlled document becomes official, and must be used as the only reference for that activity

4.2. Form – a controlled document used to convey reference information, or designed to allow recording of data to support pharmaceutical production and related activities

4.3. QA-controlled document – any Standard Operating Procedure (SOP), form, or other document subject to QA review and approval, controlled issuance, controlled change, revision control, and archive security

4.4. Revision history – record of all changes that have occurred to a document, and the reasons for those changes

4.5. Standard Operating Procedure (SOP) – a written document that describes activities necessary for cGMP compliance for pharmaceutical product manufacturing, packaging, testing, or distribution.

5. REFERENCE DOCUMENTS

5.1. Procedures for changing documents are described in SOP _____ "Document Change Process."

5.2. Training on new or revised documents is described in SOP _____ "Training Documentation for New or Revised Documents."

(Note to Reader: Examples of these SOPs are not included in this publication at this time. These SOPs should include standard internal procedures for the activities of document changes and document training, respectively. If you would like to review the ***Institute of Validation Technology****'s SOP template product line, visit www.ivthome.com for more information.)*

Your Company's Name	**Standard Operating Procedure**	*Effective Date:* August 15, 2002
Document Number: QAP-001-01	*Title:* Document Control System	*Page:* 2 of 4

6. PROCEDURE FORMAT

6.1 An established template for the format of procedures is available from the QA Document Control group, and must be used for the generation of new SOPs.

6.2 All SOPs will have a standard format that includes the following components:

6.2.1 Descriptive, but not long, title

6.2.2 Final approval that includes Document Preparer, Department Approver, and QA final approval

6.2.3 Revision history – a table that includes a brief description of the changes occurring in each version, along with justification for each version change

6.2.4 Purpose – a statement on the reason for the document

6.2.5 Scope – a statement identifying any limits associated with the activities covered by the procedure

6.2.6 Definitions – a definition for any new terms or terms requiring clarification

6.2.7 Responsibilities – a statement identifying any specific responsibilities outlined in the procedures

6.2.8 Requirements – detailed statements outlining the specific requirements or obligations included in the document

7. PROCEDURE NUMBERING SYSTEM

7.1 All SOPs and forms will comply with the following numbering system:

7.1.1 The numbering system to be used is illustrated as follows:

QCS – 001 – 00

7.1.2 In this system, the first two letters identify the primary department involved. For example, a list of departments could be set up as follows:

Department Identifier	Department Name
EN	Engineering
GP	General Plant
QA	Quality Assurance
QC	Quality Control
MR	Maintenance and Repair
SP	Solids Production

7.1.3 The third digit will identify the type of document.

Department Identifier	Department Name
C	Calibration
F	Form
M	Method
P	Policy
S	Specification
X	Cleaning

(Note to reader: These are only examples. The specific numbering scheme you use may include a significantly larger number of departments or document types. This is presented merely as an example for consideration.)

Your Company's Name	**Standard Operating Procedure**	*Effective Date:* August 15, 2002
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7.1.4 The next three digits will be a chronological number. The first document of each type would be 001, etc.
7.1.5 The last two digits will be the version number. The initial version will be 00. The first revision will be 01, etc.
7.1.6 All document numbers will be assigned by the QA Document Control group.

8. DOCUMENT ISSUANCE

8.1 All new versions of a document will include a new version number. This includes minor changes made to correct typographical errors, etc. See SOP _____ "Document Change Process" for details relating to the change process.
8.2 After all document approvals have been obtained on a new or revised document, the QA Document Control group will assure that all required training has been documented. Only after verifying that training is complete, can the document be issued. See SOP _____ "Training Documentation for New or Revised Procedures."
8.3 Upon receipt of all training documentation, the QA Document Control group will determine the effective date for the document. This date will be added to the document.
8.4 Issuance of new or revised documents will include the following steps:

8.4.1 Update the document index. The update will include adding the new document, or replacing the old version from the index.
8.4.2 Removal of the previous version of the document. For paper copies, this involves physical retrieval of each old version. For electronic copies, the old version will be deactivated or removed from the active index.
8.4.3 Paper copies will be stamped with the "Official Copy" stamp. This colored ink will identify that these copies are official and active.
8.4.4 Placement of the new or revised copy in the proper locations, along with the revised index. Paper copies will be physically placed. Electronic copies will involve replacement of active files to include the new index and document.

9. ACCESS AND PRINTING OF DOCUMENTS

9.1 In general, only the "official" copies of documents should be referenced. For example, only on-line versions of electronic documents must be referenced, and only "official" stamped paper copies should be used.
9.2 Copying or printing of documents is generally not allowed. However, controlled copies may be obtained from the QA Document Control group. Printing of copies from electronic files is allowed, only if the "Uncontrolled Copy" watermark is present and clearly visible. Upon copying or printing, each document must be signed and dated by the copying/printing individual.
9.3 Controlled copies or watermark prints are only valid for reference use, and must be destroyed at the end of each working day.

(Note to reader: Control or printing of copies is a difficult topic. The activities listed in this document are listed only as an example. Some firms choose to allow liberal copying or printing of documents. Other firms prohibit any copying or printing. This section must be customized to your operation.)

Your Company's Name	**Standard Operating Procedure**	*Effective Date:* August 15, 2002
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10. DOCUMENT STORAGE AND PHYSICAL CONTROL

10.1 All original signed documents and historical records will be stored by the QA Document Control group in secured storage units.

10.2 Only individuals authorized by the QA Document Control group may have access to stored documents.

11. REVISION LOG

Revision	Date	Section(s)	Description
00		N/A	Original Issue

12. APPROVALS

Authored By:_____ Date:_____

Reviewed By: _____ Date:_____

Approved By: _____ Date:_____
Quality Unit (QU)

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Conducting a 21 CFR Part 11 Electronic Records; Electronic Signatures Gap Assessment

…of the thirty-six Part 11-related issues referenced in 483s and Warning Letters, approximately half of the citations were related or attributable to security and integrity-related issues…

by
David R. Dills
Currently, Director of Publications, Regulatory & Compliance for the Institute of Validation Technology & Advanstar Communications, Inc. At the time of the original printing Corporate Director of Technical and Regulatory Compliance Serentec, Inc.

This article will address the planning, development, execution, and follow up of a 21 CFR Part 11 gap assessment for manufacturers in FDA-regulated industry. Strategic planning precedes the gap assessment, and is a must and a prerequisite. A gap is a void, deficiency, or a systemic breakdown within a system or component. The assessment is a preplanned, thorough, orderly, and methodical approach that will uncover the gaps within a system. Many companies plan to fail because they fail to plan. Gap assessments are dictated and governed by effective planning and strategy, deliverables, execution, due diligence, timely follow-up, and yes, a defensible position with your Part 11 compliance program.

As many in Industry know or are aware of, compliance is not black and white. It is purported, alleged, and even confirmed, that a gray area does in fact exist. We have heard statements like, "compliance is the luck of the draw," or "compliance means I passed this time." Remember the Generic Drug Scandal from years' past? Look at how many compliant companies suddenly became non-compliant or out-of-control. Part 11 is a force to be reckoned with because it's here to stay, just like the other predicate rules, i.e, Part 210 and 211, Part 820, and Part 606, whereby industry is compelled to comply with the provisions set forth by the regulations.

The Part 11 Final Rule went into effect on August 20, 1997. We have had more than four years to achieve, and hopefully, maintain compliance with our systems. Docket Number 92N-0251 (Final Rule) was implemented to create criteria for electronic recordkeeping technologies, while preserving the Agency's ability to protect and promote public health. We now know that Part 11 has become a "Good Manufacturing Practice (GMP) lifestyle" for many companies. These companies know that they have to implement the technical and procedural controls that must be met if these companies choose to maintain records electronically and use electronic signatures.

However, we also know that many companies are struggling with Part 11. Recently, a poll was conducted by a software vendor that reported that Part 11 compliance remains idle. The response to this recent poll is shown in *Figure 1*.

Ironically, Part 11 was developed in conjunction with industry over a period of six years. As we know, virtually all of the rule's requirements had been suggested by industry comments to that "famous" July 21, 1992 Advance Notice of Proposed Rulemaking. Amazingly, FDA only received 49

Figure 1

Software Vendor Part 11 Compliant Poll Statistics

Percentage	Response
75 Percent	Had begun putting in place measures to become compliant with the regulation, but are only in the early stages.
11 Percent	Had most or all systems 21 CFR Part 11-compliant. Respondents also believe compliance with Part 11 is an enormous undertaking, procedurally, administratively, and financially.
61 Percent	The estimated economic impact on their organizations of total Part 11 compliance would be substantial.[1]

comments on the proposed rule at that time. Many industry comments were received with the recent releases of the Part 11 guidance documents, e.g., glossary, validation, and time stamps. It appears that there is now significantly more collaboration and interfacing with the Agency on this subject matter.

Introduction

Be cognizant of the fact that many companies will have different approaches for defining, developing, implementing, and conducting a gap assessment. However, the gap assessment should accomplish the same objective consistently, identifying the weaknesses, as well as the strengths within your system. Here is a truncated version of the key elements involved:

- Determine the level of compliance
- Identify the weaknesses and strengths in the information available on the computerized system or area of focus
- Determine if the computerized system must comply with Part 11
- Use a checklist or comparable documentation for conducting the gap assessment
- Provide documented justification (substantiate your rationale) why some systems are or may be exempt from Part 11
- Follow up with remediation and appropriate corrective actions
- The gap assessment report will usually have an introduction, background, scope, acceptance criteria, identified systems, summary of findings, and other comparable elements.

Background

The gap assessment should be a straightforward process if a team-based approach is employed. It is important that key personnel from Quality Assurance (QA), Information Technology (IT), operations, Regulatory Affairs (RA), and other areas deemed appropriate be active participants in this process.

The gap assessment is not considered a true audit per se. However, some companies do use the term assessment and audit interchangeably. An audit is a planned, independent, and documented assessment to determine whether agreed upon requirements are being met.[2] A quality audit is a systematic and independent examination and evaluation to determine whether quality activities and related results comply with planned arrangements, and whether these arrangements are implemented effectively and are suitable to achieving objectives.[2] Nonetheless you are looking for gaps, i.e., voids or deficiencies within your system or program, and then defining and implementing the necessary remedial actions. This is similar to quality auditing, because the results are reported to management, and are used to make managerial or executive decisions concerning potential corrective actions. The purpose is to assess all computer-related systems that support GMP areas for compliance with the company's computer validation policy and operational procedures, i.e., Standard Operating Procedures (SOPs). Then you assess all computer-related systems that support GMP areas for compliance with Part 11. After this step, you initiate and implement remedial action plans, and do what is necessary and required to make the system compliant.

One approach that can be taken and pursued by a company is the following series of events for conducting a gap assessment. However, these assessments are customizable, as well as the checklists that will be used. One should tailor these assessments to the individuality of the system or facility:

- Team formation
- Review of Part 11: review documentation and the regulations
- Assessment: conducted by a specific department, the team approach, or by sites if it's a multi-site company
- Remediation: this requires planning, execution, and follow-up
- Quality and project plan: companies often develop and use these plans

- Update inventory: comprehensive inventory of all computerized systems, e.g., laboratory operations, Research & Development (R&D), quality, manufacturing, IT, and other required areas
- Develop an assessment questionnaire to all system users
- Provide a detailed summary and executive summary
- Remediation and corrective action plan
- Status reporting: should be conducted in a timely manner to ensure that deliverables are met

As the gap assessment process evolves, here are some fundamental questions that should be considered to help facilitate the decision-making process that is Part 11 compliant or even applicable in certain cases:

- Does the system perform or is it involved in a GMP function?
- Does the system interface with other GXP (GMP, [Good Manufacturing Practice], GCP [Good Clinical Practice], and GLP [Good Laboratory Practice]) systems?
- Does the system capture GMP data?
- Is the system used to make GMP decisions?
- Does the system store GMP data?
- Is the GMP task confirmed electronically?
- Does the system generate "printed" data?
- Are the data and document(s) signed after being printed?
- Does the system allow for data to be transmitted and viewed?

A logical, orderly, and strategic execution is critical to remediating "legacy" computer systems following a gap assessment. The goal is to be honest and thorough in your analysis, and in the steps taken to remedy any gaps. Areas that need to be reviewed include a budget, sufficient security, i.e., whether an audit trail is necessary, and, the validity of electronic signatures and archives. Hopefully, the gap analysis has revealed what you need to investigate. If the information is not available electronically, then maybe it should be. Is it in a database? If not, make it. Create reports on how systems exist – and where and how they fail.

In addition, identify common problems. Once you have identified a solution, you will be required to make an investment in the remediation and the costs associated with this endeavor. The driving factor is a business approach, with some of the same motivators that we see repeatedly; faster, better, and cheaper. Companies also need to recognize that SOPs will not solve every problem. There are many questions a company must ask. The risk of doing nothing is obvious, e.g., loss of data, data changed unknowingly, or system failures. This is why the two key words – integrity and security – are such critical and pivotal components of Part 11. You have to look at risk, and the price of compliance versus price of noncompliance for your company. How much risk is the company willing to assume, and is the big question: "Do you have a defensible position?"

Retirement of data is another concern. Some questions come to mind, such as: What do you do with existing data? Archive it? What will be the medium for storage? Who will have access? What are your policies for access? Another key decision is whether to pursue data migration, or to explore a total replacement. The cost of data migration can be more than the original system cost in certain cases. If replacement is the choice, then the vendor should have a compliance statement and the company should not hesitate to request it. The compliance statement may include validation of the hardware and software used, and possibly details of customization and training. Compliance statements will vary from vendor-to-vendor.

A remediation process might also require a modification of a company's SOPs or the creation of new SOPs. System codes may have to be changed to make it compliant. A software's lifecycle is certainly relevant. One positive benefit of the Y2K process, over two years ago, was that it created a myriad of ways to go through your system and identify errors. An additional option is to add codes to such software to record and/or monitor your system. Different codes and monitoring techniques will vary with companies. Determining the cost of remediation is also multi-faceted. Costs can involve additions to the database such as; new hardware, customization of software, validation, training, and development. It's quite possible you will run through several scenarios to determine costs. Hopefully, the gap analysis has revealed what you need to investigate.

Some companies will employ and use this model or approach for conducting a gap assessment. Again, companies determine the best and most practical, effective, and suitable approach to meet their objectives. Before we go any further, let's look at the big picture.

Four major areas of concern include:

❶ Conduct a comprehensive inventory of your computerized systems
❷ Identify the systems that support GMP areas
❸ Conduct the gap assessment (or analysis)
❹ Develop and execute the remediation plan

For the gap assessment approach in the preceding paragraph, a company will desire or require that the gap assessment cover or expand on the following elements:

- Documented system functionality and its intended use
- Documented evidence how the system works
- Documenting the specific areas subject to Part 11
- Reviewing all test plans and test results, which need to ensure traceability
- Validation, which means, documented proof and evidence that Installation Qualification (IQ), Operational Qualification (OQ), and any other validation testing was performed, and the documentation is current and accurate.

Other documentation that will be targeted during the gap assessment after the company observes gaps within the system may include:

- SOPs: design and development (system development lifecycle), security, backup, disaster, contingency planning, operations, training, and configuration management
- Organizational flowcharts to ensure that personnel have the necessary education, training, and experience

Nonetheless, another approach may include the following elements:

- Develop lists, such as a questionnaire, worksheet, and other templates that will facilitate the process. Some companies use a procedural matrix or spreadsheet listing all computer-related policies and procedures.
- Perform gap analysis (assessment)
- Identify remedial options
- Develop "interim" remedial actions
- Develop a master plan

It's becoming clearer that a conventional gap assessment approach uses comparable or equivalent terminology, and even the same prescribed methodology and technique. The checklist or spreadsheet shown in *Figure 2*, which is a brief example, should be used as the tool for facilitating the process for determining whether Part 11 requirements are being met. If not, then assigning the appropriate corrective action or actions to remedy the situation is required.

Why has Part 11 become such a hot topic in the industry? Here are two examples of some of the reasons why:

Recent Warning Letters have shown a blood bank that transferred electronic information to a hospital that did not have a validated electronic records system. During the process, codes for the blood donations were transposed, indicating the units had passed contamination testing and were usable, when in fact they had not been tested. As a result, seven units of untested blood were released to the public. Another example cited in the Warning Letter is that the company's computer system, called the XYX, lacked proper validation protocols, and complete and accurate records of the results were not maintained. Inadequate system security also was observed during the recent inspection, and one employee was observed, "to have utilized

Figure 2

Part 11 Gap Assessment Checklist or Spreadsheet – Example

Requirement	Assessment Result	Corrective Action
11.10(a) Validation of systems to ensure accuracy, reliability…	System XYZ for the clinical trials database is still pending validation because…	Validate the system and document rationale why system was not validated per the master plan
11.10(e) Computer-generated, time-stamped audit trails exist…	System ABC has audit trail and record changes, and not obscure previously recorded information.	None
11.50(3) Signature manifestation – meaning (review, approval, authorship, etc.)	System 1-2-3 was observed not to have a meaning associated with the signature	Modify to ensure that "meaning" is linked to the signature at all times.

another person's computer access to enter data" into the recordkeeping system.

Some of the general problem areas that FDA has observed related to Part 11 include, but are not limited to, the following:

- Legacy e-systems less secure than traditional paper
- Record integrity principles and forgotten practices
- Falsifications facilitated
- Barriers erected to FDA inspections
- Implementation given to IT alone (now known as the "disconnect syndrome")
- Failure to keep current with standards and enabling technologies
- Blind acceptance of shrink-wrap
- Resistance to change
- Poor network security (passwords posted to directory, network administrator unqualified, all users have system "admin" privileges)
- Poor password controls
- Unvalidatable systems
- No audit trail
- Failure to record laboratory data

Again, this is a non-inclusive list of areas of concern. However, it can be asserted that over the past four years, of the thirty six Part 11-related issues referenced in 483s and Warning Letters, approximately half of the citations were related or attributable to security and integrity-related issues, which are real concerns and issues.

The gap assessment will (or should) identify the voids and weaknesses within your system or company. However, one area that deserves honorable mention is that of validation. Software validation is establishing by objective evidence that all software requirements have been implemented correctly and are traceable to system requirements. This definition has been observed at various industry conference presentations. Another well known FDA definition is as follows:

> *"Software validation is confirmation and provision of objective evidence that software specifications conform to user needs and intended uses, and that the particular requirements implemented through software can be consistently fulfilled."*[3]

It's a foregone conclusion that Part 11 and validation are inseparable for the most part. Why? Because you need to validate the computerized systems to ensure accuracy, reliability, consistent intended performance, and the ability to discern invalid or altered records. This is why you validate first and then pursue Part 11 compliance.

Nonetheless, when preparing to conduct a gap assessment, a company should consider the following activities, which is another approach, but similar to what we have already discussed:

- Discuss the positive and negative experiences associated with Part 11 at your company, especially the "I" word – interpretation.
- Discuss the items learned (or assumed) since the regulation and guidance documents were released.
- Management support is critical
- Develop and implement a Part 11 training and educational program for the Part 11 task team
- Review company policies, operational procedures, SOPs, and FDA updates (review the Preamble)
- Develop a Part 11 plan (legacy plan in this case)

As with any plan, you must have a purpose, scope, deliverables, approvals, etc., and maybe acceptance criteria. Some companies will identify and assess legacy systems subject to Part 11. Develop a remediation plan, obtain management and QA approval, monitor and report progress and bottlenecks, and then control all changes to the plan – treat it as a controlled document subject to revision control. An example of a progress report may resemble the table shown in *Figure 3*.

A gap assessment checklist or spreadsheet can be quite simple to develop. The emphasis is that if a Part 11 requirement does not apply, one should not denote the space or area with just the famous, "N/A" response. You should clarify in writing why Part 11 does not apply for the official record. This is also viewed as being prudent and analyzing your process or system. This conveys assurance and confidence that you understand your system.

When conducting a gap assessment, one has to be cognizant of the fact that any software-driven process or application controlling the quality and production system, needs to be included within the scope of the assessment. The following are just some of the examples that need to be taken under consideration:

- Programmable Logic Controllers (PLCs)
- Distributed Control Systems (DCS)

Figure 3

Example of a Progress Report for a Part 11 Gap Assessment

Overall Schedule	Assessments	Remediation Plan Completed
Analytical Laboratory System	1/5/02	2/25/02
Production System	2/17/02	4/2/02
Research & Development Laboratory	3/9/02	5/23/02
Quality Assurance Data/Inspect/Test System	6/5/02	7/23/02

Systems	Number of Systems	Number Assessed	Number Compliant
Analytical Laboratory	30	20	15
Production	50	24	8
Research & Development Laboratory	10	4	2
Quality Assurance Data/Inspect/ Test System	20	11	7

- Supervisory Control and Data Acquisition (SCADA)
- Laboratory Information Management Systems (LIMS)
- Clinical trials management database systems
- Electronic Documentation Management Systems (EDMS)
- Building Automation Systems (BAS)
- Enterprise Resource Planning (ERP)
- Materials Resource Planning (MRP)
- MP-2 (Facilities/practice maintenance system)
- Complaint handling software systems
- Calibration management systems
- Commercial Off-the-Shelf (COTS) software programs
- Special inspection and testing equipment
- Laboratory equipment and testing instrumentation

This author reviewed a computer system validation project and compliance plan last year for a major pharmaceutical manufacturer. This company demonstrated that they knew exactly what they had within their system, and what necessary actions were required to bring the system and company into a state of compliance. The total number of pages comprising this plan was more than 75. *Figure 4* is a section from that plan with purged confidential and sensitive information. However, the outline will look very similar to what has been written thus far.

Gap assessments may also help with the legal concerns associated with Part 11. This assessment process can and does provide a vehicle or tool to train and educate key personnel involved in the Part 11 compliance strategy process. Some of the concerns or general comments include the following:

- Companies wishing to use e-signatures must "certify" that the e-signatures used in their system are intended to be the legally binding equivalent of the signer's handwritten signature. FDA requires that companies make a single certification for all current and future employees. This will have implications for the department with responsibility for certification. Employees will need to appreciate that their e-signature on company records could carry a criminal penalty under 18 U.S.C. §1001 if the information is later determined to be false.
- Part 11 will also present challenges for companies in the context of FDA inspections. The first challenge will be in providing timely access to records for an investigator. However difficult it may be to locate and produce old paper records in a timely fashion, older versions of e-records may present significantly more difficult challenges. The Part 11 preamble indicates that FDA may need to inspect hardware and software – this may cause headaches for companies that move to new systems.
- FDA expects companies to have computer systems that allow investigators to review e-records for as long as they are retained, which could be a long time. Companies will need to ensure that those records can be located and accessed with appropriate technology. Failure to turn over required records can have serious consequences, including criminal penalties.

Gap assessments should help achieve Part 11 compliance for most companies if conducted in accordance with the company's game plan, with predefined and preapproved procedures, and the required buy-in by all parties and approvals. Unfortunately, there are no guarantees. However, as stated earlier, compliance is not black and white, which is why companies need to be in compliance, and operating

Figure 4

Computer System and Validation Project and Compliance Plan Example

Section XX. Electronic Record/Electronic Signature (ERES) Sub Team

Team Leader:	John Doe
Principle Objective:	Harmonization of ERES guidelines across the site.
Key Milestones:	The milestones listed below are essential to the completion of this sub-project-{referring to?}. Key activities are listed for each milestone, however, this does not represent an all-encompassing list. Please refer to the Sub Team Gantt Chart for all activities.
Milestone A:	Identify all existing ERES procedures
Activity 1:	Collect information from all departments in technical operations, IT, and quality management to identify all ERES methods in use.
Prerequisites:	None
Deliverable:	List all current ERES guidelines, procedures, and standards.
Activity 2:	Establish one ERES assessment process
Prerequisite:	Activity 1 (one) complete
Deliverable:	One company XXX ERES assessment procedure, including an ERES assessment tool
Activity 3:	Train users of assessment process
Prerequisites:	Activities 1 (one) and 2 (two) complete
Deliverable:	Training records, trainer users
Milestone B:	Assessment phase
Activity 1:	Create master site ERES assessment plan
Prerequisites:	None
Deliverable:	Site master ERES assessment plan
Activity 2:	Create individual assessment teams in each organization and assign members
Prerequisites:	Assignment of team members by management (Trained team members [A-3])
Deliverables:	None
Activity 3:	Create individual organization assessment plan
Prerequisites:	Activities 1 (one) and 2 (two) complete
Deliverable:	ERES assessment plan
Activity 4:	Assess systems using approved ERES assessment tool
Prerequisites:	QA approved assessment tool and procedure (A-2)
Deliverables:	Individual systems assessments
Activity 5:	Write a remediation plan for each non-compliant system
Prerequisites:	Activities 1 (one) and 2 (two) complete
Deliverable:	ERES action plan assessment templates
Milestone C:	Remediation process
Activity 1:	Develop remediation plan
Prerequisites:	Compliance summary for individual organizations
Deliverable:	Plan for the remediation of non-compliant systems

Note: There are details and other background information associated with this plan. This example was provided to demonstrate the degree of planning and execution required by this pharmaceutical manufacturer.

in a state of control. FDA is scrutinizing computerized systems now more than ever. Industry has to be proactive. This past fiscal year ending September 2001, FDA had conducted 18,649 inspections and audits. In the fiscal year 2000, FDA conducted 15,146 inspections and this equated to 1,154 warning letters issued, 36 seizures, one civil penalty, 3, 716 recalls, 44,612 detentions, two prosecutions, and 421 arrests with 353 convictions. Industry needs to understand that there is a price to be paid for noncompliance, and if a company's systems are out-of-control, then the company is out-of-control.

This article introduced some of the most fundamental steps and activities involved and associated with Part 11 gap assessments. We have learned that companies have different approaches for conducting gap assessments. However, we also share common denominators with our gap assessment approaches. We must conduct the following activities:

- Strategic planning
- Determine the level of compliance that we are seeking
- Identify the weaknesses and strengths in our computerized systems
- Conduct an inventory of our systems
- Determine if the system must comply with Part 11
- Conduct the assessment using a checklist or spreadsheet
- Provide documented justification if certain systems are exempt from Part 11
- Implement and execute a remediation plan
- Conduct the required follow-up as warranted.

Furthermore, focus on assessment and analysis where specifics are more integral to the process. Project stages are logical and sequential to an extent, going from assessment to analysis to remediation to production to maintaining compliance. Initially in an assessment, the original inventory may be quite large, and then it will become more manageable. An assessment is a team effort and a reflection of corporate policy. Communication, of course, is key. A template should be established that addresses each and every sentence of Part 11. Your assessment should prioritize, and then create a master plan with reliable data. FDA is very concerned that companies have such a plan. The plan should be realistic, as you have seen in some of the Warning Letters. Gap assessments are tools that should work for the company and not against, in order to achieve your Part 11 compliance goals and objectives. ❑

About the Author

David R. Dills is Director of Publications, Regulatory & Compliance for the Institute of Validation Technology, a division of Advanstar Communications, Inc. and serves on advisory boards for other trade groups. He has served as an Industry Consultant, with emphasis on validation, training, assessments, regulatory affairs, inspections, submissions, and compliance. He has been involved within the FDA-regulated industry for more than nineteen years in the areas of Quality Assurance, Quality Engineering, Validation, Regulatory Affairs/Compliance, and Corporate/Operations Management on behalf of well-known manufacturers and service providers. His areas of expertise include, defining and implementing validation programs, supplier certification programs, Quality System, cGMP and validation training, auditing, policy and procedure development and deployment activities, project management, risk management and analysis, ISO 9001/13485, Gap Assessments, Computer and Software Validation/IT Network, Part 11 Gap Assessments and Remediation, MDD 93/42/EEC, change control, quality tools, statistical techniques, design control programs, CAPA, risk management/assessment, regulatory submissions, international regulations, FDA Mock and PAI Inspections, compliance activities with sample accountability, worked with companies under consent decree and CIA (corporate integrity agreements) under OIG, and other FDA-related activities. He also provides advisory input to companies to determine if the systems are designed, deployed and maintained in a sustainable compliance and validation environment. He currently serves on the Faculty Advisory Board for the Pharmaceutical Training Institute and Editorial Advisory Boards for Software Quality Professional and the Institute of Validation Technology (IVT), publisher of the Journal of GXP Compliance and Journal of Validation Technology. He serves on the Readers' Board for Medical Device & Diagnostic Industry and Medical Product Manufacturing News and was nominated and accepted for inclusion into the 2004-2005 Strathmore's Who's Who of Professionals. He has authored and published numerous validation and regulatory/compliance-related articles, commentaries and technical guides, and is an accomplished global industry speaker and presenter. He has academic degrees in Environmental Science and Biology. He currently serves as Advisor for the American Society of Quality's Section 1506 and as a former Chair and Co-Chair and is an active member of the Biomedical Division, RAPS, PDA, ISPE, and other industry groups. He may be contacted at 904-519-8040 or cell at 904-614-3220. The fax number is 904-519-9810 and e-mail is ddills@advanstar.com.

References

1. *Genetic Engineering News*, November 15, 2001.
2. J.P. Russell. *The Quality Auditing Handbook*. ASQ Quality Audit Division. 1997.
3. General Principles of Software Validation; Final Guidance for Industry and FDA Staff, issued on January 11, 2002 (supersedes Version 1.1, dated June 9, 1997).

Suggested Reading

1. *Validation Times* (Insight on GMP Validation: News, 483/warning letter analysis, compliance tips) – multiple issues in 2001.
2. FDA. Code of Federal Regulations, Title 21, Part 11. "Electronic Records; Electronic Signatures: Final Rule." *Federal Register*, (March 20, 1997).
3. Fields, T. "Impact of 21 CFR Part 11 on Computer-Related System Validation." *Journal of Validation Technology*. Vol. 7, No. 4 (August) 2001.
4. Grunbaum, L. "Remaining in a 21 CFR Part 11 Compliant State." *Journal of GXP Compliance*. Vol. 6, No. 3 (April) 2002.
5. FDA. Fiscal Year 2001 Report, Office of Regulatory Affairs.

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Environmental Control Programs: What They Are and What They Should Include

The QSR [Quality System Regulation] requires in 820.70(e) that every manufacturer establish and maintain procedures to prevent contamination of product or equipment. These process specifications are established by the manufacturer…

by
Cynthia Green, RAC
President
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What is an Environmental Control Program?

An Environmental Control Program (ECP) is a comprehensive program that includes a written plan that outlines the steps in developing, establishing, implementing, and monitoring the environmental controls necessary to ensure that products are consistent, reproducible, and reliable. The ECP includes the following elements: facility design, construction, and operation, utilities, cleaning, raw materials and components, personnel, waste flow, preservative systems, and environmental monitoring. Environmental monitoring is merely one tool that is used to measure the program's success. The ECP also includes the procedures and documentation generated in support of the program.

An ECP plan can be developed in newly established companies prior to the transfer of the first product from development into production and Quality Control (QC). The plan, in this case, will serve as a "roadmap" for the identification and creation of the procedures, training, records, and supporting activities required to establish the ECP.

For existing companies, an ECP plan can be developed as an evaluation tool. The plan, in this case, can serve as an assessment for the adequacy of the procedures, training, and record-keeping to support a balanced ECP. A balanced program requires facility and utility design, raw material selection, cleaning procedures, personnel/material flows, preservative systems, and environmental monitoring procedures that result in a minimal risk to product and patient safety that is consistent with product and regulatory requirements.

Objectives of the Environmental Control Program

The objective of an ECP is to integrate the elements of the ECP into a balanced environment that will ensure the performance and reliability of the product consistent with regulatory requirements.

What are the key steps in developing an ECP?

❶ Define the objectives and scope of the ECP.
❷ Assign preliminary responsibilities.
❸ Prepare a plan to identify and evaluate each environment, capture responsibilities, and make assign-

ments. Refer to the sample ECP provided. Refer to the list of recommended SOPs to support the plan.

❹ Obtain senior management approval to fund and support the EPC.

❺ Execute the plan.

❻ Verify completion of the assignments, and monitor completion to ensure effectiveness. Refer to the example audit checklist located on page 16 of this article.

Elements of the Environmental Control Program

To further understand the elements that comprise the ECP, it is important to define and describe each element, and the role it plays in balancing the environment.

Implementation of the Environmental Monitoring (EM) Program requires that the following preliminary requirements be considered:

(a) Product requirements. Products require a variety of different environmental controls. It is important to evaluate the potential risk from the environment, and assess its potential impact on the product and its intended use.
(b) Regulatory requirements. There are regulations and guidance documents available that can serve as excellent sources of information.
(c) Standard industry practice. Information is available through conferences, seminars, websites, organizations, and communication with colleagues.

1. *Facility design, construction, and operation.* The focus for this area will be on the operation of the facility, and the ability to minimize potential contamination originating from the materials used for construction (ceiling material, paint, cabinets, shelving, flooring, etc.); the Heating, Ventilation, and Air Conditioning (HVAC) system (particulates [viable and nonviable], separation between air handling units [supply and return air], pressurization, air changes, etc.); pest control, and general building maintenance and repair.

For medical devices, the Quality System Regulation (QSR) Manual addresses contamination control under excerpt 6: Buildings and Environment. The manual reads:

> *The QS regulation requires in 820.70(e) that every manufacturer establish and maintain procedures to prevent contamination of product or equipment. These process specifications are established by the manufacturer to ensure that finished devices will meet the company's quality claims. Typical device examples are: in vitro devices that are not contaminated with microbes, detergents or rodenticides; circuits that are not contaminated with flux; implants that are not contaminated with body oils and certain implants that are not contaminated with pyrogens. Pyrogens are substances that cause fever in humans, and they arise primarily from cellular debris of gram-negative bacteria. Certain implants such as orthopedic implants are not required or expected to be pyrogen free. Other devices are required to be nonpyrogenic including: transfusion and infusion assemblies, devices that come in contact with circulating blood or cerebrospinal fluid, intraocular lenses and the surgical instruments used in their implantation, and any device labeled as "nonpyrogenic." Manufacturers should carefully control the environment in which such devices are manufactured and processed to minimize contamination with bacteria or establish a procedure for cleaning the devices.*

For drug products, 21 CFR Part 211 Subpart C addresses buildings and facilities. Section 211.42 describes the required design and construction features. Specific citations include:

(a) Any building or buildings used in the manufacture, processing, packing, or holding of a drug product shall be of suitable size, construction and location to facilitate cleaning, maintenance, and proper operations.
(b) Any such building shall have adequate space for the orderly placement of equipment and materials to prevent mixups between different components, drug product containers, closures, labeling, in-process materials, or drug products, and to prevent contamination. The flow of components, drug product containers, closures, labeling, in-process materials, and drug products through the building or buildings shall be designed to prevent contamination.
(c) Operations shall be performed within specifically defined areas of adequate size. There

shall be separate or defined areas or such other control systems for the firm's operations as are necessary to prevent contamination or mixups during the course of the following procedures:

(1) Receipt, identification, storage, and withholding from use of components, drug product containers, closures, and labeling, pending the appropriate sampling, testing, or examination by the quality control unit before release for manufacturing or packaging.
(2) Holding rejected components, drug product containers, closures, and labeling before disposition.
(3) Storage of released components, drug product containers, closures, and labeling.
(4) Storage of in-process materials.
(5) Manufacturing and processing operations.
(6) Packaging and labeling operations.
(7) Quarantine storage before release of drug products.
(8) Storage of drug products after release.
(9) Control and laboratory operations.
(10) Aseptic processing, which includes as appropriate.
(i) Floors, walls, and ceilings of smooth, hard surfaces that are easily cleanable.
(ii) Temperature and humidity controls.
(iii) An air supply filtered through high-efficiency particulate air filters under positive pressure, regardless of whether flow is laminar or nonlaminar.
(iv) A system for monitoring environmental conditions.
(v) A system for cleaning and disinfecting the room and equipment to produce aseptic conditions.
(vi) A system for maintaining any equipment used to control the aseptic conditions.

(d) Operations relating to the manufacture, processing, and packing of penicillin shall be performed in facilities separate from those used for other drug products for human use.

One of the first steps in the evaluation and assessment of the potential impact of the facility on the environment is to document the facility design criteria. One method is to prepare a table, such as the following:

Facility Design Criteria

Room Number	Area	Activities	Adjacencies	Proposed Classification[1]	Pressurization[2] Relative to Adjacent Hallway (Or Area)	Comments Concerns

Instructions for completing the table:

1. Enter the room number for each specific room or area.
2. Enter a brief description or the name of the room or area.
3. Briefly describe the activities or operations that take place in that area. Ensure that the list of activities is complete.
4. List the rooms or areas that are adjacent to the room or area.
5. Indicate the proposed classification for the area.
6. Indicate the pressurization differential between the specific room or area, and the adjacent rooms or areas.
7. Indicate any special concerns or challenges regarding the room, operations, classification, or adjacencies.

Once the areas are identified, and the required classifications for each area have been determined, an evaluation can be performed on the physical requirements for each area. A table similar to the following example can be used in the evaluation.

Table References

1. The classification referenced in this column relates to nonviable particulates only, and is used to refer to "relative cleaniness." It is not intended to set a standard for humidity, temperature, number of High Efficency Particulate Air (HEPA) (filters), air changes, etc.
2. Pressurization is either positive or negative, and a minimum of 0.05 inches of water at "+," 0.10 inches if water for "++."

Facility Design Considerations[3]

	Class 10,000	Class 100,000	Microbiologically Controlled/ Unclassified	Uncontrolled/ Unclassified
Ceiling	Epoxy coated or plastic polyester coated drywall; smooth, easy to clean, and resistant to cleaning agents. Solid ceiling recommended. If paneling is used, panels must be gasketed and sealed.	Cleanable tiles (or solid ceiling) are recommended. Non-shedding material.	Not required	Not required
Walls	Plastic, epoxy coated drywall or paneling; smooth, easy to clean, resistant to cleaning agents.	Same	Same	Not required
Floors	Coved, seamless, sealed to wall.	Easy to clean, sealed coving.	Same	Not required
Windows	Required for monitoring, flush, no ledges (unless slanted).	Same	Not required	Not required
Doors	Doorframes and jams must be sealed, sweeps in place, self-closing.	Same	Same	Not required
General	No protrusions, ledges, exposed piping allowed.	Same	Not required	Not required
	Access doors in walls and ceilings limited.	Same	Not required	Not required
	No drains.	Same	If present, must have break or backflow preventer; connection between process and waste drains must be avoided.	Not required
Benches, work surfaces, shelving	Cleanable, non-shedding, resistant to cleaning agents and chemicals. No wood.	Cleanable, non-shedding, resistant to cleaning agents and chemicals. Wood is not recommended. If used, it must be sealed.	Not required	Not required
Gowning	Hair net, lab coat, shoe covers, facial hair covering, and gloves.	Same. In areas where there is no potential for product exposure, gloves are not required.	Same; however, no gloves.	Not required

Table References

3. "Sterile Manufacturing Facilities." ISPE Baseline Pharmaceutical Engineering Guides for New and Renovated Facilities. Vol. 3. January 1999.
D. Vincent. "Validating and Establishing a Routine Environmental Monitoring Program." Journal of Validation Technology. *Vol. 4 No. 2. February 1998.*

Additional steps in the evaluation include the preparation of a list of observations made from a facility "walk about." A detailed list of items of concern that may have a potential impact on the environment is a useful tool in achieving an adequate level of control. Some items of particular concern include obvious dirt and dust, peeling paint, gaps under exterior doors, gaps in the ceiling tiles, and open exterior windows/doors. The mechanical systems must also be verified to "as-built" conditions. It is difficult, if not impossible, to determine how the environmental conditions can be improved if the mechanical systems are not verified as being accurate.

Prepare and carefully review product, personnel, equipment, and waste flows. Evaluate the flows in light of the potential for mix-up and contamination with regard to the desired area activities, classifications, adjacencies, pressure differentials, and special concerns.

Identify the potential risks and prioritize activities for improvement.

2. *Utilities.* The emphasis in this area will be on the operation of the utility systems, such as water, air, vacuum, and gases. There will be a heavy focus on the water system, since water is considered a critical ingredient for product.

Utilities, such as purified water and Water-For-Injection (WFI), compressed air, nitrogen, and other process gases are considered raw materials or starting materials by most regulated companies. It is likely that these materials will have direct product contact. The quality of these materials is every bit as critical to the products quality as a key chemical or ingredient. The utilities also serve as support systems to ensure equipment and processes are adequately controlled to provide reliable and reproducible products. Key support systems include electrical services, potable water, vacuum, heating and cooling systems, and plant steam. These process support systems generally do not have direct product contact; however, they may have a significant effect on the product's quality.

Utility systems must be validated and routinely monitored to ensure they are capable of providing the required quality of material or service. Monitoring may require routine sampling and testing of the resulting water, air, gas, etc. The systems must be well-maintained to ensure reproducible and reliable operation. Whether the maintenance is performed in-house or by a contract organization, well-documented procedures must be in place, and the frequency of required maintenance must be performed according to established schedules. Where recognized standards exist, those standards should be applied.

3. *Cleaning*. The focus for this area will be general facility cleaning, whether provided by external personnel or by internal personnel, equipment cleaning, preparation and storage of cleaning solutions, maintenance of cleaning equipment, such as mops, buck, etc., and procedures used for cleaning.

For new companies, review the regulatory requirements for establishing a cleaning program. Discuss personnel qualifications, written procedures, selection of cleaning agents, and recordkeeping.

Review the facility cleaning procedures used by in-house personnel, as well as procedures utilized by contract services. Review records and contracts that are in place with the contract services to ensure that adequate records are being kept and the contract is being followed. Determine if the procedures are being followed, and if they specify the cleaning agents and the preparation of those cleaning agents. Ensure that the cleaning agents, their concentration, and the procedure for use are consistent with those that have been used in the cleaning validation.

Review the written procedures for equipment cleaning. Ensure that the purpose of the cleaning is consistent with the agent chosen for use. For example, if the objective of the cleaning is to sanitize a piece of equipment, ensure that the cleaning agent chosen is designed to accomplish the desired sanitization by reviewing the technical literature available from the supplier. There is an excellent article discussing the selection of disinfectants written by Vivian Denny, et al. that appeared in the PDA *Journal of Pharmaceutical Science & Technology* entitled "Elements for a Successful Disinfection Program in the Pharmaceutical Environment" (Vol. 53, No. 3. May/June 1999). Additional reference articles on cleaning appear in the **Institute of Validation Technology** (**IVT**) *Cleaning Validation: An Exclusive Publication* featuring articles from William Hall and other cleaning experts.

Cleaning agents must be selected based on the nature of the material to be removed, extent of cleaning and/or disinfection required (i.e., is the objective of the cleaning to reduce the quantity of the material present or to sanitize the item being cleaned?), chemical and physical properties of the residues to be cleaned, surface and materials of construction of the item to be cleaned, and potential hazards to the users.

For an ideal disinfectant, the cleaning agent should be nonspecific in microbial action, nontoxic, odorless, harmless to tissue, noncorrosive to surfaces, inexpensive, and not inactivated by organic material.

During selection of cleaning agents, one must consider what organisms are potentially present and at what level. Other considerations include whether odor or fumes may affect the process, and whether the cleaning agent may adversely affect the materials to be cleaned.

To evaluate the categories of cleaning valida-

Cleaning Agent	Material (of the Item to be Cleaned)	Material (to be Removed)	Purpose of the Cleaning Step	Cleaning Procedure

tions required, a matrix approach is recommended.

Using the table, items that need to be cleaned can be grouped according to similarities. Once the groups have been identified, determine which items are the most difficult-to-clean within each group by observing the cleaning process, discussing cleaning with individuals responsible for the cleaning, and evaluating the potential for inadequate cleaning. Focus the validation efforts on those items determined to be the most challenging to clean. This approach has been shown to be practical and effective.

Documented cleaning procedures should include the specific agent validated for use, its expiration date, precautions during handling, instructions for preparation, set or contact time required, and whether there is a rinse required. The procedure must also specify the quality of water to be used to prepare the cleaning solution. It is recommended that purified water at a minimum be used for preparing cleaning solutions.

Personnel assigned to cleaning must be adequately trained in written cleaning procedures, requirements for gowning, if required, and record-keeping. Once personnel have been trained, effectiveness checks should be conducted to confirm the training. Records should be monitored frequently to ensure they are accurate and complete.

4. *Raw* materials and components. The emphasis in this section will be on those raw materials and components that are likely (or somewhat likely) to contribute bioburden to product. This material category includes both product ingredients, as well as items that have direct product contact, such as cleaning and sanitizing agents.

It is common for both diagnostic and pharmaceutical companies to utilize a wide variety of materials that may not be fully characterized or well-defined. A material may have:

- Inherent variability as a result of its starting materials or the process parameters.
- Biological origin.
- Bioburden associated with either its starting materials or its processing.

As a result of the potential impact on finished products, the raw materials that may have an effect on products as a result of bioload, must be identified. These materials must be carefully evaluated and controlled. This may require the addition of added controls on the supplier to maintain and deliver these selected materials within established specifications for bioburden or sterility. Special packaging, handling, sampling, and storage may be required to maintain the material's integrity.

According to 21 Code of Federal Regulations (CFR) 211.84:

> *"Testing and approval or rejection of components, drug product containers, and closures. (d)(5). Each lot of component, drug product container, or closure that is liable to contamination with filth, insect infestation, or other extraneous adulteration shall be examined against established specifications for such contamination. (b)(6). Each lot of component, drug product container, or closure that is liable to microbiological contamination that is objectionable in view of its intended use shall be subjected to microbiological tests before use."*

According to 21 CFR 211.113:

> *Control of microbiological contamination. (a) Appropriate written procedures, designed to prevent objectionable microorganisms in drug products not required to be sterile, shall be established and followed. (b) Appropriate written procedures, designed to prevent microbiological contamination of drug products purported to be sterile, shall be established and followed. Such procedures shall include validation of any sterilization process.*

5. *Personnel.* The focus in this area is personnel hygiene. There are seven (7) elements that affect personnel hygiene in an environmentally controlled facility.

(a) Separation of activities. There are different requirements for each zone or separate area, including control of access, personnel flow, and protection of the cleanest area from those areas less clean.

(b) Gowning. Clothing must be appropriate for the product, and be based on relative risk. Personnel training in proper gowning technique must be provided.
(c) Cleaning and disinfection. There must be a comprehensive plan for the complete facility. The plan must be written, documented, and effective.
(d) Training. Personnel training must be performed, documented, and effective. Training should include basic principles of microbiology, aseptic technique, cleanroom classification, validation, potential contamination sources, contamination controls, quality systems, and cGMPs.[4] The depth of training in each of these areas should be dependent on the assignments and responsibilities of the individuals being trained.

Training can be performed using in-house personnel, consultants, videos, publications, outside seminars and workshops, or using software-based training. Software-based programs are gaining popularity and have been shown to provide very effective training. One company offering "e-based" training is Eduneering (www.Eduneering.com). Eduneering offers a wide variety of courses applicable to regulated companies. As Bill Hall (Hall and Associates) described:

> *"..the Internet poses a wonderful opportunity to take the training to the company rather than always have to take the individual to the training. The new technology of the Internet gives us the technical mechanism to do just that. It also allows the individual to stay at work and still train at their convenience. So the advantages are that it can be done at the work site and at the convenience of the individual. It eliminates the travel expense."*

Regardless of the method used to deliver training, the training program must include the following:

■ Training Plan. This includes a plan for each new employee, as well as a renewal plan for existing employees. The plan and a schedule for retraining should be reviewed with the employee at each evaluation interval.

■ GMP training. This training should be performed at least once yearly. In the event there are audit findings that warrant focused training, special sessions should be conducted to address identified weak areas.

■ Job specific training. On-the-job training should be performed by having the employee first observe, then perform the work under close supervision until the trainer determines that the trainee can perform the work independently.

■ Safety training. All employees should be trained in applicable safety requirements prior to work assignments that may pose a potential risk to themselves or others.

■ Training on procedures. This training should be performed as new procedures are introduced, and as existing procedures are revised.

(e) Motivation. Personnel have a significant impact on the cleanliness of the environment in which they work. They must be motivated to adhere to established procedures, communicate with others, perform self-inspections, and be continually aware of the potential impact they may have on the environment.
(f) Written procedures. The procedures must be easy-to-follow, clearly written, accessible, and complete in order to ensure that the procedure will be performed reproducibly, and to the same standard each time.
(g) Monitoring. Monitoring must be used to confirm that required parameters are and remain within established limits. The limits should be based on the relative risk to the product. The techniques used for monitoring should provide meaningful results.

6. *Waste flow.* The focus for this area will be the flow of waste from its origin to the staging area, and from the staging area to the waste pickup location. The collection site, method of transporting from the collection site, container used for the transport, pathway taken to reach the staging location, etc. must be reviewed for potential impact on the product.

Environmental regulations may have a significant impact on the waste water systems designed and implemented for individual products. Wastewater may require neutralization, inactivation, etc. prior to release to the drain.

Spill procedures must be established based on the potential risk of the spill, and the adjacent areas that may be impacted by the spill. Spill drills should be performed to ensure that the procedures for handling spills of significant size can be effectively handled. Safety equipment should also be

strategically located in the areas of highest probability for a spill. Personnel should be trained in the spill procedures.

The flow of waste through the facility may have a potential impact on the environment, and must be carefully evaluated. Totes, carriers, carts, or other means of containment are commonly used for transporting waste. Waste transport can be scheduled before or after production. A passthrough may be used for transitioning waste from one area to another.

Ensure that the areas for holding waste are appropriate for the waste being held. The containers used must be adequate in size and number to prevent overfilling. Access to the waste holding areas should be limited to authorized personnel only. The hold time should be as short as possible to avoid unnecessary buildup prior to pickup or disposition.

7. *Preservative systems*. The focus for this section will be on the selection of the preservative, its concentration, and the formulation in which it is used. Preservative Effectiveness Testing (PET) must be conducted on groups of products with identical or nearly identical formulations. In addition to PET, an environmental challenge study should also be conducted. This second study is a challenge of environmentally isolated organisms spiked into the product. The product is then evaluated over time for both microbial growth, as well as actual product performance.

The object of preserving product is to ensure that the product is both safe and stable. Studies must be conducted to determine the effective concentration to preserve the product during processing, storage, and use by the customer.

Microorganisms are unique and have a wide variety of metabolic capabilities. There are microbes that can be grown essentially everywhere, and can utilize any organic and some inorganic compounds as substrates for growth. Do not make any assumptions when selecting a preservative system.

The choice of a preservative must be based on the formulation of the product and the physiochemical characteristics of the preservative. There are known incompatibilities that will have a significant impact on the effectiveness of the chosen preservative. According to the Guide to Microbiological Control in Pharmaceuticals,[5] the ideal preservative should have the following characteristics:

(a) Broad spectrum of activity.
(b) Effective and stable over a broad range of pH.
(c) Compatible with the formulation and packaging material.
(d) Does not affect the physical properties of the product (i.e., color, clarity, odor, flavor, viscosity, texture).
(e) Suitable oil-to-water ratio to ensure effective concentration in the aqueous phase.
(f) Inactivate microorganisms rapidly to prevent microbial adaptation.
(g) Safe.
(h) Compliant with regulatory requirements.
(i) Cost effective.

The optimum preservative must be chosen based on all of these factors. Testing must demonstrate and document the selection, stability, and effectiveness of the product, as well as the preservative.

8. *Environmental Monitoring*. The focus here is to monitor the success and adequacy of the program. Monitoring must be done at frequent intervals. The frequency of sampling should be based on the product requirements. The testing must include both viable and nonviable particulate monitoring. Action and alert levels should be established that are consistent with the data generated, as well as the product requirements.

According to FDA's Medical Device Quality Systems Manual,[6] an appropriate system for regular monitoring should be established and maintained for each of these factors to be controlled for a given operation. This will ensure that equipment is performing properly, and that the quality of the environment is within specifications. When a particle count Class is specified, monitoring of airborne particulates is usually done with an air sampler. Monitoring of work surfaces for microbes (colony forming units) may be done with surface contact plates or settling plates. However, settling plates should not be used for monitoring when horizontal laminar air flow is used. They are ineffective for this type of flow.

All sampling should be done per written procedure and the data recorded. Further, periodic inspections of environmental controls and documentation of the inspections are required by the QS regulation. The inspection checkoff form or other record should be kept simple.

An evaluation of the HVAC system is necessary to determine how the system was designed, is cur-

rently operating, and what quality of air it is capable of delivering. Once the system is known and understood, then an evaluation of the cleaning procedures can be performed. Unless the cleaning program is reliable and reproducible, the EM program cannot be effective.

In addition to HVAC and cleaning procedures, gowning and personnel training should be reviewed for potential weakness or opportunities for improvement. A gap analysis should be performed and corrections made. Once the support systems are in place, the EM program can be implemented.

The EM program is comprised of the following elements:

(a) Sampling plan (sampling locations and justification for selection of the locations).
(b) Schedule for frequency.
(c) Equipment and validation.
(d) Supplies.
(e) Microbiology laboratory.
(f) Test methods and method validation.
(g) Data collection and trending tools.
(h) Alert and action levels.
(i) Investigations and corrective actions.
(j) Effectiveness checks.
(k) Recordkeeping and reporting requirements.

There are several excellent resources published on environmental monitoring. The most recent is the Technical Report No. 13 (Revised) from the Parenteral Drug Association (PDA) entitled *Fundamentals of an Environmental Monitoring Program*. Another was published by the **Institute of Validation Technology** in February, 1998 entitled *Technical Guide: Validating and Establishing a Routine Environmental Monitoring* by David Vincent.[7]

Conclusion

An ECP must be supported with control systems, and carefully balanced with facility design, cleaning procedures, personnel, flow patterns, and environmental monitoring. The program must be developed based on product requirements, existing environmental constraints, and what can "practically" be performed, managed, and controlled on a routine basis. Use logic. Understand the underlying rationale behind the program, and the relative risks associated with each element that supports the program. Focus on the objectives of the program, and ensure adequate control is in place to meet those objectives.

There is no substitute for a common-sense approach to the design and implementation of an ECP. ❑

From FDA's Medical Device Quality Systems Manual

Any practices or factors from the following list that the manufacturer has deemed appropriate and elected to use should be specified and routinely performed or followed. Some additional factors that should be considered when planning and using a controlled environment include:

- Proper attire and dressing anteroom
- Controlled use of, and entry into, controlled areas
- Prohibiting eating, drinking, smoking, or gum chewing
- Preventing use of lead pencils
- Regulating the storage of glassware and containers
- Preventing or controlling the cutting, tearing or storage of cardboard, debris, etc.
- Cleaning the room and production equipment per written procedure
- The original design and cleaning of work surfaces and chairs
- Selecting correct furniture and eliminating all nonessential equipment
- Controlling room air quality (amount of particulates, pressure, velocity, and exchange rate)
- Eliminating electrostatic charges by controlling work surface composition or grounding
- Ensuring cleanliness of raw materials, components and tools
- Controlling the purity, sterility, and nonpyrogenicity of process water and maintaining prefilters, HEPA filters, and electrostatic precipitators

References

1. The classification referenced in this column relates to nonviable particulates only, and is used to refer to "relative cleanliness." It is not intended to set a standard for humidity, temperature, number of HEPAs, air changes, etc.
2. Pressurization is either positive or negative, and a minimum of 0.05 inches of water at "+," 0.10 inches of water for "++."
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6. FDA's Medical Device Quality Systems Manual: A Small Entity Compliance Guide. December, 1996.
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Suggested Reading

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9. D. W. Vincent. "Validating and Establishing a Routine Environmental Monitoring Program for Clean Room Environments." *Journal of Validation Technology*. Vol. 4, No. 2 (1998).
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11. Baseline Pharmaceutical Engineering Guide Series. "Introduction to Biotech." ISPE Conference. June 5-6, 2000.
12. FDA's Medical Device Quality Systems Manual: A Small Entity Compliance Guide. December 1996.
13. Technical Report No. 33. "Evaluation, Validation, and Implementation of New Microbiological Testing Methods." *Journal of Parenteral Science and Technology*. Vol. 54, No. 3 (2000).
14. International Standard ISO 14644-1. "Cleanrooms and associated controlled environments-Part 1: Classification of air cleanliness." 1999.
15. International Standard ISO 14644-2. "Cleanrooms and associated controlled environments-Part 2: Specifications for testing and monitoring to prove continued compliance with ISO 14644-1." 2000.
16. International Standard ISO 14644-4. "Cleanrooms and associated controlled environments-Part 4: Design, construction and start up." 2001.

Environmental Control Program Standard Operating Procedures

1. Environmental Controls
2. Water Monitoring and Trending
3. Viable Air Monitoring and Trending
4. Nonviable Air Monitoring and Trending
5. Surface Monitoring and Trending
6. Personnel Monitoring and Trending
7. Personnel Training and Qualification
8. Facility Cleaning Procedures
9. Equipment Cleaning Procedures
10. Product Bioburden Testing and Trending
11. Personnel Flow
12. Waste Flow
13. Personnel Hygiene
14. Gowning
15. Facility Change Control
16. Mechanical Rounds
17. Environmental Failures and Investigation

Environmental Control Program Audit Checklist

	Yes	No	Comments
Facility Design and Operating (e.g., Construction Materials, Heating, Ventilation, and Air Conditioning [HVAC])			
Is there a facility qualification protocol and test report for the current facility?			
Is there a current floor plan?			
Is there a current mechanical drawing for the HVAC?			
Has the HVAC been validated?			
Is there a written preventative maintenance agreement for the HVAC system?			
Has Preventive Maintenance (PM) been performed and documented? If so, when _____			
Does the work completed conform to the signed agreement?			
Are the PM records audited by Quality Assurance (QA)? If so, when were the records last audited?			
Were all adverse findings satisfactorily resolved?			
Is there a current "zone map" indicating what air handlers are designated for what rooms/areas?			
Is the HVAC design adequate to provide separation of clean from less clean activities?			
Are there start up and shut down procedures in shared production areas?			
Is there a written changeover procedure to ensure adequate cleaning and inspection of shared areas prior to initiating a new job?			
Are the walls, floors, and ceilings in good condition? (For example, is there any peeling paint, exposed wood, cracks, open joints, damaged tiles, walls, ceiling tiles?)			
Do production areas have pipework, light fixtures, ventilation ducts, or other fixtures that are difficult-to-clean?			
Are drains constructed in a manner that allows ease of cleaning?			
Is there routine cleaning of drains that is documented?			
Is the facility properly constructed to support the Environmental Control Program (ECP)?			
Is the facility designed to allow proper cleaning, maintenance, and other necessary operations?			
Are there procedures in place for routine inspection and documentation of the facility's general condition?			
Does the facility appear clean and well maintained?			
Are there areas of clutter where cleaning would be difficult?			
Are items stored off of the floor allow ease of cleaning?			
Do corners appear clean?			
Is there visible dirt or dust on ledges, window seals, door jams, or similar surfaces?			
Is there a documented pest control program?			
Is the facility designed and maintained in a manner to prevent the entry of insects and animals?			
Are pesticides described in the Standard Operating Procedure (SOP)? Are the pesticides approved for use in food or other FDA-regulated environments?			

Environmental Control Program Audit Checklist

	Yes	No	Comments
Facility Design and Operating (e.g., Construction Materials, Heating, Ventilation, and Air Conditioning [HVAC])			
Does the designated individual who reviews the pest control service provided to ensure that only approved agents are used? Is this review documented?			
Is there an established procedure for monitoring and recording the temperature in the areas used for storage, handling, and processing product?			
Has acceptance criteria for temperature been established?			
Are there data to demonstrate that the products will not be affected by temperature that falls below or rises above the established range?			
Are data available that determines what other environmental conditions must be controlled, such as light, humidity, ventilation, etc.?			
Do areas used for production and Quality Control (QC) have restricted access to prevent individuals not working in those areas from entering?			
Are restrooms and breakrooms separate from production and QC areas?			
Are there procedures in place to prohibit preventive maintenance activities, repair, or construction while production is in process, or at times when there may be a potential risk of product contamination?			
Are there documented inspections of environmental controls that indicate systems are functioning properly?			
Utilities (e.g., Water, Air)			
Are there written procedures for routine monitoring of water at all points of use?			
Are there additional sampling locations, such as before and after key system components?			
Is water sampled in a manner consistent with the use of the water from that port?			
Is microbial testing performed at least weekly?			
Are the microbes detected submitted for identification?			
Are results from the water testing routinely evaluated and trended?			
Are there written procedures that describe the evaluation and trending that is performed?			
Are there written procedures for the reporting of deviations and nonconformances of water test results?			
Are there established acceptance levels for microbial contamination?			
Are there written procedures for action to be taken when the levels are exceeded?			
Are nonconformances reported to the Corrective and Preventative Action (CAPA) program with documented investigations, corrective action, and follow up?			
Are there written preventive maintenance procedures?			
Does the PM include resin and filter changes? How often are the filters changed? The resin?			

Environmental Control Program Audit Checklist

	Yes	No	Comments
Utilities (e.g., Water, Air)			
Are there contractor SOPs on site that describe the treatment of resin?			
Are the results from the PM documented?			
Is there a written contract with the service provider?			
Has the contractor been qualified and routinely monitored under written purchasing control policies and procedures?			
Is the water system routinely sanitized? How often is the sanitization performed? Is this performed by the service contractor or by in-house personnel?			
Are there procedures for sanitization?			
Does the procedure ensure that all surfaces in the water system are sanitized?			
Was the sanitization procedure validated for effectiveness and removal of the sanitizing agent?			
Does the procedure include a check for the removal of the sanitizing agent? Is the result from the check documented?			
Is there a procedure that describes the water system design, including all components, preventive maintenance procedures, sampling points, sanitization procedure, and its frequency?			
Are there “dead legs” that have a potential for contaminating the water system?			
Are hoses attached to the points of use?			
Are there procedures in place for the removal, replacement, and sanitization of the hoses?			
Has the current water system been validated?			
Did the validation account for seasonal variations? When was the validation completed?			
Have there been changes to the water system since the original validation was completed, and if so, has the water system been revalidated?			
Manufacturing Processes (e.g., Product Exposure)			
Has a risk assessment been performed to determine the potential impact from the environment on the product?			
Are bulk containers left uncovered during processing or storage?			
Are personnel working in areas where product is uncovered or exposed to the environment properly gowned? For example, is all hair completely covered? Are arms exposed? Are beard covers used? Are labcoats fully buttoned? Are shoecovers worn?			
Is product ever exposed to the outside environment, such as open doors, windows, etc.?			
Are food, plants, or animals kept in areas where product is handled, stored, or tested?			
Are product, personnel, and waste flows designed and practiced in a manner to minimize the potential for cross contamination?			

Environmental Control Program Audit Checklist

	Yes	No	Comments
Manufacturing Processes (e.g., Product Exposure)			
Is there a process for reporting deviations that may potentially have an adverse impact on the product from an environmental perspective?			
Are these deviations monitored on a regular basis for trends?			
Is waste handled, transported, and stored in a manner that will minimize potential product contamination?			
Are the outside surfaces of containers cleaned prior to transport into clean areas? For example, are the lids of containers cleaned?			
Do production instructions require that a physical check be performed to confirm equipment is visibly clean prior to its use?			
Is this check documented in the device history record or batch record?			
Is there a maximum time limit specified between equipment use and when it was last cleaned?			
Are there written procedures that will ensure that mix-ups, damage, deterioration, contamination, and other adverse effects do not occur during the handling and storage of product (in-process and final product)?			
Cleaning (e.g., Facility and Equipment)			
Are written procedures in place to describe the cleaning of all manufacturing areas and QC laboratories?			
Do the procedures specify approved cleaning agents?			
Do the procedures include instructions for proper gowning during cleaning?			
Is there a map or floor plan that specifies what mops are to be used to clean which areas?			
Is there a procedure for the cleaning, replacement, and treatment of mops and buckets after use?			
Is cleaning of all areas documented in a manner that records the date, cleaning agent used, area cleaned, which items in each area were cleaned, and the person(s) responsible for the cleaning?			
Are cleaning records audited by QA on a routine basis ?			
How often are the records audited, and is the audit documented?			
Have the cleaning personnel been trained in the current procedures?			
Is the training documented?			
Was there an effectiveness check for the training?			
Is there a contractual agreement that includes the requirement to notify the company (being cleaned) when cleaning personnel are changed?			
Does the agreement include notification if there is a change in equipment?			
Are the current SOPs being followed as they are written?			
Are all cleaning agents NOT specified in the SOPs removed from each production and laboratory area?			
Are there Material Safety Data Sheet (MSDS) documents stored in areas where the cleaning agents are used?			

Environmental Control Program Audit Checklist

	Yes	No	Comments
Cleaning (e.g., Facility and Equipment)			
Has the effectiveness of the cleaning agents been validated?			
Is equipment appropriately designed and placed to facilitate maintenance, adjustment, cleaning, and use?			
Are there procedures for cleaning both major and minor equipment?			
Do the procedures specify the cleaning agents?			
Have the equipment cleaning procedures been validated?			
Have the assigned individuals been trained in the written procedures?			
Is the cleaning of equipment recorded in a logbook?			
Have potential contaminants of equipment been identified, and considered in the selection of cleaning agents?			
Does the clean equipment visually appear to be clean and dry?			
Is it stored in a manner to prevent re-contamination?			
Is the cleaning status posted on the equipment?			
Is there a time indicated as to when the equipment has to be recleaned prior to use?			
Have the methods used to detect and/or measure the effectiveness of the cleaning been validated?			
Are cleaning procedures sufficiently detailed to describe the cleaning agent, its concentration, its set time, the rinse process, quality of water, etc.?			
Have individuals involved in the cleaning of equipment been trained, and is the training documented?			
Is the equipment cleaning validated using three consecutive lots or cleaning cycles?			
Did the validation focus on difficult-to-clean areas?			
Was rinse sampling used to monitor the effectiveness of cleaning?			
Were swab samples taken when there was risk of contaminants remaining on surfaces?			
Was the cleaning of multi-use equipment validated to prevent carry over?			
Was the cleaning of dedicated equipment confirmed in the validation?			
Was the removal of detergents, if used in cleaning, validated?			
Were the individuals involved with sampling during the validation trained, and was the training they received, documented?			
When failures occur that suggest cleaning errors, problems, etc., is there an investigation, corrective action, follow up, and reporting to CAPA?			
Are there procedures that describe the consequence of cleaning failures on product release?			
Is there an ongoing surveillance program to monitor the cleaning program?			
Is the surveillance of the cleaning program documented?			
Are there procedures in place to manage the addition of new equipment or products with respect to its impact on the cleaning procedures and validation of those procedures?			

Environmental Control Program Audit Checklist

	Yes	No	Comments
Raw Materials and Components (e.g., Inherent Bioburden Load)			
Is there a comprehensive list of raw materials and components used in manufacturing each product?			
Have the raw materials and components, likely to have microbial contamination, been identified?			
Are data from previous bioburden testing of those materials available?			
Is there a written procedure for the sampling and handling of raw materials and components that include precautions to minimize potential contamination from personnel performing the sampling?			
Is there a written procedure for the storage of raw materials and components that include precautions to minimize potential contamination that could occur during storage?			
Examine the raw material and component storage areas to determine compliance with the SOPs. Are the SOPs being followed as written?			
Is there a current stability program that includes bioburden testing of raw materials and/or components that are likely to have bioload?			
Is there a written procedure for the testing of bioburden for raw materials and components?			
Have bioburden alert and action levels been established for raw materials capable of contaminating final product or promoting microbiological growth?			
Are data available to support the assigned alert and action levels?			
Has the procedure for testing bioburden been validated with respect to accuracy, precision, specificity, limit of quantitation, limit of detection, linearity, range, ruggedness, and repeatability?			
Has the equipment required for bioburden testing been validated?			
If outside testing is used, has the contract laboratory been qualified in a manner consistent with purchasing control SOPs?			
Are data monitored and evaluated for trends?			
Is there a written procedure that describes the procedure for monitoring and trending of the data?			
Personnel (e.g., Traffic Flow, Training)			
Have personnel involved with the handling and processing of product been trained in the potential adverse impact from the environment?			
Have personnel been trained in proper gowning technique?			
Has the training received been documented?			
Is there a procedure that prevents personnel who have not received training from working in production?			
Are traffic flow patterns established in a manner to minimize potential product mix-up and contamination?			
Are there written personnel hygiene procedures in place?			
Do these procedures include health, hygiene practice, and gowning requirements?			

Environmental Control Program Audit Checklist

	Yes	No	Comments
Personnel (e.g., Traffic Flow, Training)			
Are requirements in place that ensure no person with potentially infectious disease or open cuts, wounds, or lesions engage in production activities?			
Are food and drink prohibited from production areas?			
Are precautions taken to prevent the hands and arms of operators from contaminating the product?			
Are personnel instructed to wash their hands prior to entering and after exiting the production areas?			
Have personnel been trained in the proper procedure for washing hands?			
Preservative Systems (e.g., Agents Chosen and Concentration)			
Is there a current listing of products that contain preservatives?			
Is the exact quantity of each preservative listed for each product?			
Have studies been completed for each product that include U.S. preservative challenge studies?			
Have there been formulation changes since those studies were performed?			
In addition to the United States Pharmacopeia (USP) challenge studies, have challenge studies been performed with environmental organisms isolated from the facility, water, raw materials, and/or product?			
Have suppliers of the preservatives changed since the studies were performed?			
Have studies been completed to demonstrate equivalence of the new supplier to the one previously used?			
Are there alternate manufacturers (actual producers of the material, not alternate distributors) for the preservatives used?			
Microbiology and Quality Control Laboratories			
Is there an established Environmental Monitoring (EM) program?			
Is this program written and sufficiently detailed to ensure the program is capable of demonstrating control of the environment?			
Is sampling performed at least weekly in areas where product is exposed?			
Are the results monitored and trended?			
Are there procedures that describe the monitoring and trending?			
Are there established alert and action levels?			
Are there data to support the established levels?			
Are the results reported to CAPA with investigation, corrective action, and follow-up?			
Are corrective actions completed in a timely manner?			
Are the personnel assigned to the monitoring trained in the procedures?			
Is the training documented?			
Did the training include an effectiveness check?			
Is the training current?			

Environmental Control Program Audit Checklist

	Yes	No	Comments
Microbiology and Quality Control Laboratories			
If sampling is performed using an outside contractor, has the contractor been qualified according to established supplier qualification procedures?			
Is the equipment used under a calibration and maintenance program?			
Has the media used been stored and handled in a manner consistent with the manufacturer's labeling?			
Has the media been used within its expiration dating?			
Was the media incubated for a time and temperature consistent with the manufacturer's recommendation?			
Is there a designated individual responsible for the review and acceptance of the contractor's data?			
Is the review of the data documented?			
Are positive and negative controls incubated with each batch of environmental plates/strips?			
Is there a requirement for the identification of microorganisms? How often is identification performed?			
Is the identification requirement documented?			
Is there a procedure for handling data that represents an environmental baseline change? For example, when microorganisms are identified that have not previously been isolated?			
Quality Assurance			
Is there an audit program that includes routine review of the laboratory used for bioburden testing of product and incubation/enumeration of environmental monitoring samples?			
Has an on-site audit been performed within the last 12 months?			
Were observations noted that required further investigation, corrective action, or follow up?			
Were these items resolved within a reasonable timeframe?			
Are service contractors involved with the handling, transport, and disposition of waste included in the supplier qualification program?			
Have the companies been audited within the last 12 months?			
Have adverse findings been resolved in a timely manner?			
Are procedures in place for the routine monitoring of waste haulers?			
Have cleaning records been audited within the last three (3) months?			
Is there a written procedure for handling environmental excursions or environmental deviations?			
Is there a procedure for reporting alerts to manufacturing?			
Is there a procedure for the investigation and corrective/preventative action for deviations?			
Does the Material Review Board (MRB) review environmental deviations and nonconformances?			
Are environmental trend reports submitted to management? How often?			
Is software used to generate trend reports validated?			
Is QA involved with the trending of environmental data?			

Environmental Control Program Audit Checklist

	Yes	No	Comments
Quality Assurance			
Does QA routinely audit environmental monitoring source documents?			
Is there a QA requirement for revalidation of critical systems when any significant change or alteration occurs?			
Is there a procedure for the restriction of production when environmental levels are exceeded?			
Are conditions for stopping production clearly defined in the SOP?			
Does the SOP designate the individual who is responsible for stopping production?			
Are requirements for resuming production clearly defined in the SOP?			

Environmental Control Program Definitions

Action Level:	A level that, when exceeded, indicates a process has drifted from its normal operating range. A response to such an excursion should involve a documented investigation and corrective action.
Alert Level:	A level that, when exceeded, indicates a process may have drifted from its normal operating condition. Alert levels constitute a warning, but do not necessarily warrant corrective action.
Cleaning:	Chemical or physical means used to remove soil and/or microorganisms from surfaces.
Continuous monitoring:	A process of data collection where conditions are monitored continuously. In most United States applications, this definition implies, "during production." For International Organization for Standardization (ISO) applications, this means twenty-four hours per day, seven days a week.
Controlled Area:	Area where unsterilized product, in-process material, and containers/closures are manufactured or prepared. Different types and levels of controlled areas exist and, depending on their function, different class designations and resulting conditions are maintained.
Corrective Action:	A response to an excursion or failure.
Critical Area:	Area where sterilized products or containers/closures are exposed to the environment.
Dynamic Monitoring:	Monitoring of an environment during normal operations, e.g., equipment operating, personnel present, and the process or simulated process is ongoing. Per the European Union (EU) and ISO documents, this is synonymous with an operational condition.
Environmental Control Parameters:	Conditions and corresponding measurements as associated with facilities and equipment utilized in the manufacturing process that may impact the identity, strength, quality, or purity of a product. Among such parameters are airflow rates and patterns, pressure differentials, materials, personnel flow, temperature, relative humidity, as well as non-viable and viable particulates.
Non-viables:	A term used in reference to particulates that are not capable of living, growing, or developing and functioning successfully; "unable to divide."
Risk Analysis:	A determination made to assess the hazards and consequences associated with an occurrence.
Viable:	Capable of living.

Your Company's Name	**Standard Operating Procedure**	*Effective Date:*
Document Number:	*Title:* Environmental Controls	*Page:* 1 of 5

1. PURPOSE

1.1 To provide guidance concerning environmental controls at the company.

1.2 To define the elements of an Environmental Control Program (ECP) and the areas that are governed under the program.

2. SCOPE

2.1 This document applies to all company personnel involved in the ECP.

3. RESPONSIBILITY

3.1 It is the responsibility of the Program Manager to coordinate the environmental control activities of the departments and team members.

4. REFERENCES AND APPLICABLE DOCUMENTS

4.1 21 CFR 820.70(c)

4.2 ISO 9000:2000, ISO 13485:1996, EN 46001:1996

4.3 Document No. xxxx, "Corrective Action and Preventative Action (CAPA)"

4.4 Document No. xxxx, "Management Responsibility"

5. DOCUMENTATION REQUIREMENTS

5.1 None

6. DEFINITIONS

6.1 Action Level: A level that, when exceeded, indicates a process has drifted from its normal operating range. A response to such an excursion should involve a documented investigation and corrective action.

6.2 Alert Level: A level that, when exceeded, indicates a process may have drifted from its normal operating condition. Alert levels constitute a warning, but do not necessarily warrant corrective action.

6.3 Cleaning: Chemical or physical means used to remove soil and/or microorganisms from surfaces.

6.4 Continuous monitoring: A process of data collection where conditions are monitored continuously. In most United States applications, this definition implies, "during production." For ISO applications, this means twenty-four hours per day, seven days a week.

6.5 Controlled Area: Area where unsterilized product, in-process material, and containers/closures are manufactured or prepared. Different types and levels of controlled areas exist, and, depending on their function, different class designations and resulting conditions are maintained.

6.6 Corrective Action: Actions to be performed that are in SOPs, and are initiated when certain conditions are exceeded.

6.7 Critical Area: Area where sterilized products or containers/closures are exposed to the environment.

6.8 Dynamic Monitoring: Monitoring of an environment during normal operations, e.g., equipment operating, personnel present, and the process or simulated process is ongoing. Per EU and ISO documents, this is synonymous with an operational condition.

Your Company's Name	**Standard Operating Procedure**	*Effective Date:*
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6.9 Environmental Control Parameters: Conditions and corresponding measurements as associated with facilities and equipment utilized in the manufacturing process that may impact the identity, strength, quality, or purity of a product. Among such parameters are airflow rates and patterns, pressure differentials, materials, personnel flow, temperature, relative humidity, as well as non-viable and viable particulates.

6.10 Non-Viables: A term used in reference to particulates, that are not capable of living, growing, or developing and functioning successfully; unable to divide.

6.11 Preventive Action: Action taken to eliminate a potential nonconformance, defect, or other undesirable situation in order to prevent occurrence.

6.12 Risk Analysis: A determination made to assess the hazards and consequences associated with an occurrence.

6.13 Viable: Capable of living.

7. GENERAL INFORMATION

7.1 Environmental conditions reasonably expected to have an adverse effect on the quality of a product or process must be controlled. The establishment of an ECP within the company is a means of ensuring a balanced environment, as well as compliance to specified requirements for product safety, performance, and reliability.

7.2 The purpose of the ECP is to define, establish, implement, and maintain a level of environmental control that is consistent with the requirements identified. The ECP is more than just environmental monitoring. Environmental monitoring is only one tool that is used to measure the success of the program.

8. PROCEDURE

8.1 General Approach for Establishing an ECP

- 8.1.1 Define the project's scope
- 8.1.2 Obtain Executive Management approval to fund and support the project.
- 8.1.3 Assign responsibilities.
- 8.1.4 Perform a risk assessment to identify the primary level of concern.
- 8.1.5 Evaluate the identified risks for potential impact (product, personnel, regulatory, etc.).
- 8.1.6 Prepare a list of action items with target dates for completion.
- 8.1.7 Assign responsible individuals.
- 8.1.8 Prepare a work plan for each area. Capture team member responsibilities, resource requirements, regulatory risks, technical risks, and assignments.
- 8.1.9 Once actions have been completed, verify completion.
- 8.1.10 Monitor to ensure that corrective actions have been effective.
- 8.1.11 Perform both random and scheduled audits to document adherence to the established plan and compliance to applicable regulations.
- 8.1.12 Provide feedback from the audit to the CAPA program as described in monitoring procedures. (Refer to Document No. xxxx).

8.2 Overview of Elements of the ECP

- 8.2.1 Facilities design and operation
  - 8.2.1.1 Assign the responsibility for environmental control in the facility area to the Facilities Manager.

Your Company's Name	**Standard Operating Procedure**	*Effective Date:*
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8.2.1.2 Include the administration of the assignments as set forth by the Program Manager to ensure that the facility operates, and is maintained in a manner that will minimize the potential risk of product contamination originating from the materials of construction, and the Heating, Ventilation, and Air Conditioning (HVAC) system.

8.2.1.3 Evaluate and document:

8.2.1.3.1 The current status of the general condition of the facility, including general appearance, state of repair, adjacent grounds

8.2.1.3.2 The HVAC system, including zone mapping and separation of activities, and current operating condition

8.2.1.3.3 SOPs that are relevant to establishing and maintaining environmental controls. These procedures include:

(List the SOPs here for mechanical rounds, HVAC system operation and maintenance, pest control, building maintenance and repair, maintenance of lighting, and similar documents)

8.2.1.3.4 Items identified as needing improvement

8.2.1.3.5 New procedures required to support the ECP in the facilities area

8.2.2 Utilities

8.2.2.1 Assign the responsibility for utilities to the Facilities Manager.

8.2.2.2 Include the administration of the assignments set forth by the Program Manager to ensure that the utilities used in the production facility operate consistently in a manner that will minimize potential risk of product contamination.

8.2.2.3 Evaluate and document:

8.2.2.3.1 The current status of the utility systems, including state of repair and maintenance of the water, compressed air, vacuum, and nitrogen systems

8.2.2.3.2 SOPs that are relevant to establishing and maintaining environmental controls. These procedures include:

(List the SOPs here, such as water system operation and maintenance, and similar ones for the other utilities.)

8.2.2.3.3 Items identified as needing improvement

8.2.2.3.4 New procedures required to support the ECP in the utilities area

8.2.3 Manufacturing Processes

8.2.3.1 Assign the responsibility for manufacturing processes to the Production Manager.

8.2.3.2 Include the administration of the assignments set forth by the Program Manager to ensure that the manufacturing processes are performed consistently in a manner that will minimize potential risk of product contamination.

8.2.3.3 Evaluate and document:

8.2.3.3.1 Production processes with respect to potential environmental exposure and risk of contamination

8.2.3.3.2 SOPs that are relevant to establishing and maintaining environmental controls. These procedures include:

(List the SOPs here, such as filtering, handling of solutions, dispensing, bulking, or compounding, etc.)

8.2.3.3.3 Items identified as needing improvement

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8.2.3.3.4 New procedures required to support the ECP in the process area

8.2.4 Cleaning

8.2.4.1 Assign the responsibility for cleaning to the Production Manager.

8.2.4.2 Include the administration of the assignments set forth by the Program Manager to ensure that cleaning is performed consistently in a manner that will minimize the potential risk of product contamination.

8.2.4.3 Evaluate and document:

8.2.4.3.1 Cleaning processes with respect to potential environmental exposure and risk of contamination

8.2.4.3.2 SOPs that are relevant to establishing and maintaining environmental controls. These procedures include:
(List the SOPs here, such as facility, cleaning by janitorial service personnel, facility cleaning by in-house personnel, cleaning if work surfaces, equipment cleaning, preparation and storage of cleaning solutions, maintenance of mops and cleaning equipment, etc.)

8.2.4.3.3 Items identified as needing improvement

8.2.4.3.4 New procedures required to support the ECP in the cleaning area

8.2.5 Raw Materials and Components

8.2.5.1 Assign the responsibility for qualification of incoming materials to the Quality Control (QC) Manager.

8.2.5.2 Include the administration of the assignments set forth by the Program Manager to ensure that qualification is performed consistently in a manner that will minimize potential risk of product contamination.

8.2.5.3 Evaluate and document:

8.2.5.3.1 The raw materials and components that are likely or somewhat likely to contain significant bioburden

8.2.5.3.2 Procedures for testing bioburden of materials and components

8.2.5.3.3 SOPs that are relevant to establishing and maintaining environmental controls. These procedures include:
(List the SOPs here, such as bioburden testing of raw materials, stability test procedures for raw materials, etc.)

8.2.5.3.4 Items identified as needing improvement

8.2.5.3.5 New procedures required to support the ECP in the raw material area

8.2.6 Personnel

8.2.6.1 Assign responsibility for personnel to the Program Manager.

8.2.6.2 Include the administration of the assignments to ensure that personnel are trained and perform assignments consistently in a manner that will minimize potential risk of product contamination.

8.2.6.3 Evaluate and document:

8.2.6.3.1 Personnel training in gowning, aseptic processing, hygiene, traffic flow, changeover between products, etc.

8.2.6.3.2 SOPs that are relevant to establishing and maintaining environmental controls. These procedures include:
(List the SOPs here, such as gowning, hygiene, traffic flow, changeover, training, etc.)

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8.2.6.3.3 Items identified as needing improvement
8.2.6.3.4 New procedures required to support the ECP in the personnel area
8.2.7 Preservative Systems
8.2.7.1 Assign the responsibility for establishing adequate preservative systems to the Product Development Manager.
8.2.7.2 Include the administration of the assignments set forth by the Program Manager to ensure that products have been, and will be, formulated in a manner that will minimize potential risk of product contamination.
8.2.7.3 Evaluate and document:
8.2.7.3.1 Current preservative systems, and systems proposed for products in development
8.2.7.3.2 Available data on product bioburden
8.2.7.3.3 Available data on preservative challenge studies
8.2.7.3.4 SOPs that are relevant to establishing and maintaining environmental controls. These procedures include:
(List the SOPs here, such as preservative challenge testing, environmental challenge studies, etc.)
8.2.7.3.5 Items identified as needing improvement
8.2.7.3.6 New procedures required to support the ECP in the preservative area
8.3 General Maintenance of the ECP
8.3.1 To ensure compliance to the ECP, develop and implement a maintenance plan for the continual monitoring, assessment, and improvement of the ECP.
8.3.1.1 Feedback to the management review program is provided by status and activity reports generated from the maintenance plan.
8.3.2 Include the following areas in the maintenance plan:
8.3.2.1 Calibration program, including facility systems, production equipment, and test equipment
8.3.2.2 Preventive maintenance program, including facility systems, production equipment, and test equipment
8.3.2.3 Internal audit program, including random and scheduled audits of all functional areas
8.3.2.4 CAPA, including activities of the management review
8.3.2.5 Training program, including both in-house, as well as outside activities
8.3.2.6 Environmental monitoring program, including surface, viable air, and nonviable particle sampling and evaluation, as well as microbial water monitoring
8.4 Record Retention
8.4.1 Retain all appropriate ECP documentation according to the company's policies and procedures for record retention and applicable regulatory requirements. ❑

ENVIRONMENTAL CONTROL PLAN
Version: 1.0

Prepared by:	
Date:	

Plan Approvals:

Name	Signature	Date

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1.0 PROJECT OVERVIEW

1.1 Objective

The objective of the Environmental Control Project Plan ("the Plan") is to:

- outline the steps necessary to develop, establish, implement, and monitor the environmental controls necessary to ensure the company's products are consistent, reproducible, and reliable
  - to determine when and where steps are necessary to control the environment
  - to establish and provide a program that will minimize the potential for contamination of product and equipment

1.2 Scope

1.2.1 The Environmental Control Project Plan is limited in scope to_____. *(Define the scope in brief, concise, and clear terms. Specify where the program applies within the facility. To further clarify, consider adding a statement indicating where the program does not apply.)*

1.3 Intended Audience

1.3.1 Internal Departments

The Plan is intended for the following internal departments:

- Executive Management
- Engineering
- Product Development
- Production
- Quality Assurance
- Quality Control
- Regulatory Affairs
- Validation Committee

1.3.2 External Resources

The Plan is intended for the following external resources:

- Service Providers
- Consultants

2.0 REFERENCES

2.1 U.S. and International Regulatory References

2.1.1 21 CFR Parts 200, 600, and 800

2.1.2 ISO 14644-1: Cleanrooms and Associated Controlled Environments-Part 1: Classification of Air Cleanliness

2.1.3 ISO 14644-2: Cleanrooms and Associated Controlled Environments-Part 2: Specifications for Testing and Monitoring to Prove Continued Compliance with ISO 14644-1

2.1.4 ISO 14644-4: Cleanrooms and Associated Controlled Environments-Part 4: Design, Construction, and Start up

2.1.5 (Add others, as applicable.)

2.2 Standard Operating Procedures (Include complete title of SOP, the document number, and revision level.)

2.2.1 Environmental Control Plan. Document xxx, rev. xxx (Refer to example SOP.)

2.2.2 Environmental Monitoring, Document xxx, rev. xxx

2.2.3 Water Monitoring and Trending, Document xxx, rev. xxx

2.2.4 Air Viable Monitoring and Trending, Document xxx, rev. xxx

2.2.5 Non-viable Monitoring and Trending, Document xxx, rev. xxx

2.2.6 Surface Monitoring and Trending, Document xxx, rev. xxx
2.2.7 Personnel Monitoring and Trending, Document xxx, rev. xxx
2.2.8 Personnel Training and Qualification, Document xxx, rev. xxx
2.2.9 Cleaning Procedures, Document xxx, rev. xxx
2.2.10 Bioburden Testing of Product, Document xxx, rev. xxx
2.2.11 Personnel Flow/Controlled Access, Document xxx, rev. xxx
2.2.12 Facility Change Control, Document XXX, rev. XXX
2.2.13 Failure Investigations for Environmental Excursions, Document xxx, rev. xxx
2.2.14 Corrective and Preventive Actions for the Environmental Control Program, Document xxx, rev. xxx
2.2.15 Gowning Procedures, Document xxx, rev. xxx
2.2.16 Personnel Hygiene, Document xxx, rev. xxx
2.2.17 Operating and Maintenance Procedures for the General Facility, HVAC and Utility Systems (Water, Gases, etc.), Document xxx, rev. xxx

3.0 DEFINITIONS AND ABBREVIATIONS

3.1 Definitions

3.1.1 Action Level: A level that, when exceeded, indicates a process has drifted from its normal operating range. A response to such an excursion should involve a documented investigation and corrective action.
3.1.2 Alert Level: A level that, when exceeded, indicates a process may have drifted from its normal operating condition. Alert levels constitute a warning, but do not necessarily warrant corrective action.
3.1.3 Cleaning: Chemical or physical means used to remove soil and/or microorganisms from surfaces.
3.1.4 Continuous monitoring: A process of data collection where conditions are monitored continuously. In most United States applications, this definition implies, "during production." For ISO applications, this means twenty-four hours per day, seven days a week.
3.1.5 Controlled Area: Area where unsterilized product, in-process material, and containers/closures are manufactured or prepared. Different types and levels of controlled areas exist and, depending on their function, different class designations and resulting conditions are maintained.
3.1.6 Corrective Action: Actions to be performed that are in SOPs, and are initiated when certain conditions are exceeded.
3.1.7 Critical Area: Area where sterilized products or containers/closures are exposed to the environment.
3.1.8 Dynamic Monitoring: Monitoring of an environment during normal operations, e.g., equipment operating, personnel present, and the process or simulated process is ongoing. Per EU and ISO documents, this is synonymous with an operational condition.
3.1.9 Environmental Control Parameters: Conditions and corresponding measurements as associated with facilities and equipment utilized in the manufacturing process that may impact the identity, strength, quality, or purity of a product. Among such parameters are airflow rates and patterns, pressure differentials, materials, personnel flow, temperature and relative humidity, as well as non-viable and viable particulates.
3.1.10 Non-viables: A term used in reference to particulates, that are not capable of living, growing, or developing and functioning successfully; "unable to divide."
3.1.11 Risk Analysis: A determination made to assess the hazards and consequences associated with an occurrence.
3.1.12 Viable: Capable of living.

3.2 Abbreviations

3.2.1 CFR: Code of Federal Regulations

3.2.2 ISO: International Organization for Standardization

3.2.3 SOP: Standard Operating Procedure

4.0 MAJOR MILESTONES

4.1 List of Milestones

4.1.1 The major milestones include the following: (The tasks listed are for example only. Each program must develop its own list of relevant tasks.)

Task	Assigned to	Date Due
Determine environmental control requirements		
Complete preliminary actions		
Perform environmental control audit		
Complete risk assessment		
Complete action items		
Complete evaluation for effectiveness		

5.0 RESPONSIBILITIES

Assign each task to a responsible individual. The assigned individual must agree to the assignment, and the individual's immediate supervisor must authorize the assignment.

6.0 DUE DATES

Assign due dates for each task. The assigned individual, and his/her immediate supervisor must approve the date assigned. The due dates must be tracked, preferably using project management software.

7.0 TASKS AND DELIVERABLES

7.1 Tasks

7.1.1 The tasks, individual assigned, due date, and current status are indicated in the following table.

Task Description	Assigned To	Due Date	Status

8.0 DELIVERABLES

The document title with its number, responsible person, target date for completion, and current status are indicated in the following table.

Doc Title	Responsible person	Target date	Status

9.0 PROGRAM MASTER PLAN OVERVIEW

9.1 Definition of Phases

The phases of the Environmental Control Program include:

- Executive management approval
- Identification of key resources
- Preparation of the implementation plan
- Execution of the plan
- Monitoring of assignments through completion
- Verification of effectiveness

9.2 Reporting Requirements

9.2.1 The Project Leader will be responsible for preparing and issuing a monthly report, noting the progress of all assignments.

9.2.2 The status report will be distributed to _____(indicate to whom the report will be issued).

9.3 Phase End Reviews and Approvals

At the completion of each phase, a phase review meeting will be held. The meeting will be scheduled and facilitated by the Project Leader.

10.0 PROJECT TEAM ORGANIZATION

10.1 Project Team

The Project Team includes the following individuals:

Name	Title	Affiliation

11.0 PROJECT COMMUNICATION

The Project Team will meet weekly during the development and implementation of the plan. Minutes will be recorded and circulated weekly to the Project Team members.

Communication between team members will be primarily through email. The e-mail addresses and contact numbers of the team members are as follows:

Name	E-mail address	Phone #	Fax #

12.0 RESOURCES

12.1 High Level Summary to Implement the Project

The resources required to implement the plan include the following:

Responsibilities	Full-Time Employee (FTE)
Baseline Assessment and Gap Analysis	
Preparation of protocols	
Review of protocols	
Execution of protocols	
Preparation of test reports	
Review of test reports	
Calibration of equipment	

12.2 High Level Summary for Expenditures

Expenses for Implementing the Plan include the following:

Description	Est. Cost
Equipment	
Outside consultants	
Supplies	
Training	

13.0 RISK MANAGEMENT PLAN

(Examples are provided for completion of this section.)

13.1 Technical Risks

There is extensive experience within the company to support the Environmental Control Program (ECP). There are no known technical risks.

13.2 Administrative/Organizational Risks

Due to the limited resources, it may be difficult for current staff to generate, review, and approve the documents required to support the plan within the timeframe specified.

13.3 Resource Risks

Until a workload analysis has been completed, it cannot be determined if there is adequate staff to support the plan. The Environmental Control Plan will be updated when a workload analysis has been completed.

13.4 Regulatory Risks

Failure to implement an ECP may result in a Warning Letter. A Warning Letter may impact products intended for export, as well as pending regulatory submission approval. A failure to implement the program in a timely manner may also result in regulatory action against the company, that may include, and not be limited to, seizure, injunction, or civil penalties.

14.0 ASSUMPTIONS, DEPENDENCIES, CONSTRAINTS

(Examples are provided for completion of this section.)

14.1 The assumptions made include:

14.1.1 The plan will be reviewed in a timely manner

14.1.2 Those asked to perform the review will provide comments and suggested revisions to the Project Leader in a timely manner.

14.1.3 All ECP requirements have been identified.

14.2 The dependencies include:

14.2.1 Budget approval to support the plan

14.2.2 Allocation of resources to support the plan

14.2.3 Availability of consultants and service providers to assist in-house personnel

14.3 The constraints identified include:

14.3.1 Time

14.3.2 Financial resources

15.0 MONITORING AND CONTROLLING MECHANISMS

15.1 The mechanisms used to monitor and control the plan include the following:

15.1.1 Regularly scheduled meetings with the project team

15.1.2 Regular reports to senior management

15.1.3 Review and oversight by an independent auditor ❑

About the Author

Cindy Green has over 27 years of experience in the healthcare industry, and has been consulting for 10 years in the biotech, drug, and medical device areas. Cindy's recent work includes validation master plans, validation protocols/reports, quality assurance programs, environmental assessments, environmental control programs, stability programs, and preparation of regulatory submissions. Cindy has over 15 years of expertise with Center for Biologics Evaluation and Research (CBER) regulated companies, and has performed consulting services in the U.S., Europe, and Asia. In 1998, Cindy co-founded Pacific Regulatory Support (www.pac-regsupport.com) providing on-line Standard Operating Procedures (SOPs) to the healthcare industry. SOPs available include Good Manufacturing Practice (GMP)/ISO, Good Clinical Practice (GCP), and Good Laboratory Practice (GLP) documents, as well as SOPs for software and equipment service. She can be reached by phone at 425-432-8623, or by e-mail at cindynwrs@seanet.com.

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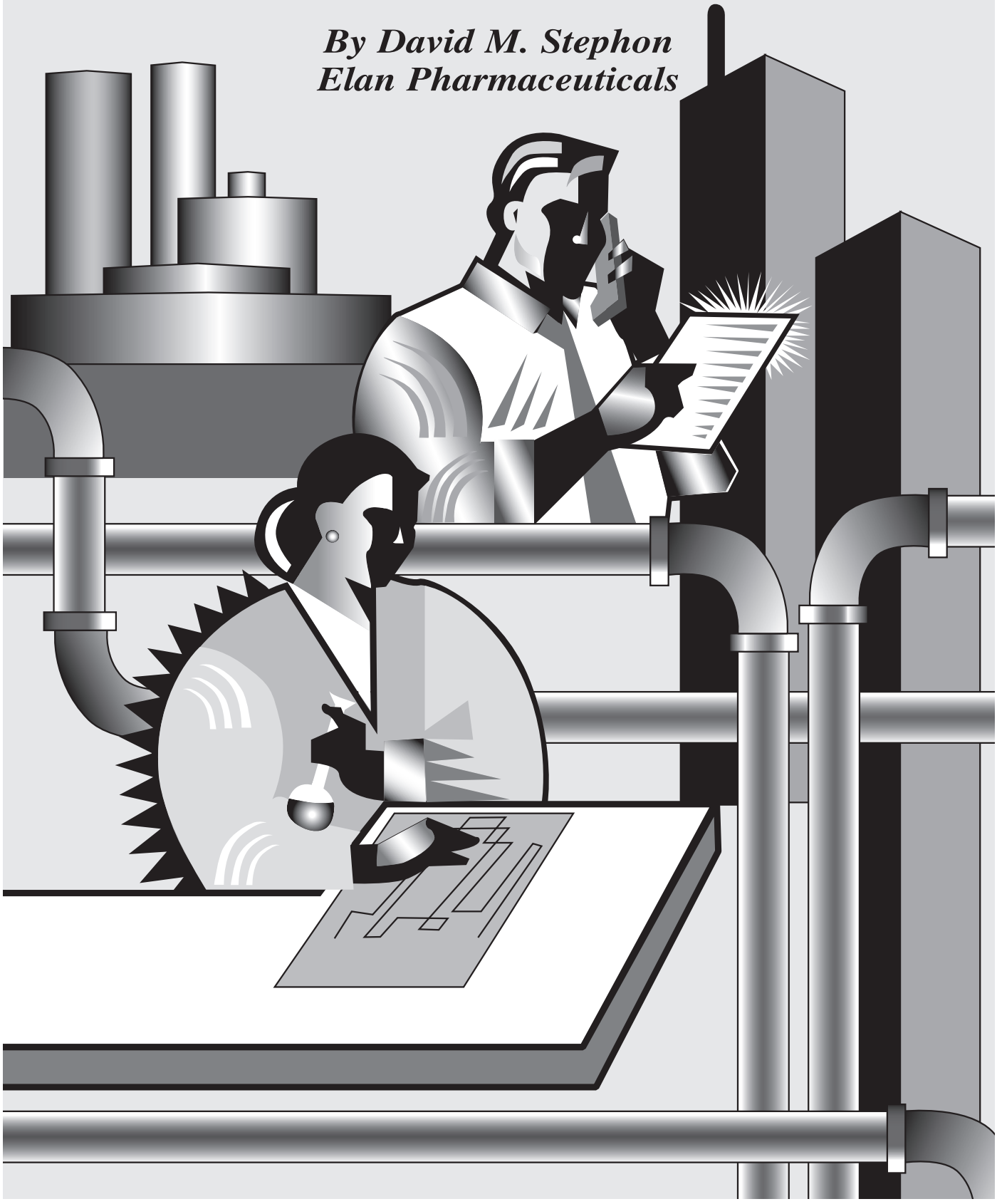
Article Acronym Listing

CAPA:	Corrective and Preventative Action
CBER:	Center for Biologics Evaluation and Research
CFR:	Code of Federal Regulations
ECP:	Environmental Control Program
EM:	Environmental Monitoring
EU:	European Union
FTE:	Full-Time Employee
GCP:	Good Clinical Practice
GLP:	Good Laboratory Practice
GMP:	Good Manufacturing Practice
HEPA:	High Efficiency Particulate Air
HVAC:	Heating, Ventilation, and Air Conditioning
ISO:	International Organization for Standardization
MRB:	Material Review Board
MSDS:	Material Safety Data Sheet
SOP:	Standard Operating Procedure
PDA:	Parenteral Drug Association
PET:	Preservative Effectiveness Testing
PM:	Preventive Maintenance
QA:	Quality Assurance
QC:	Quality Control
QSR:	Quality System Regulation
USP:	United States Pharmacopeia
WFI:	Water-For-Injection

Supplier Qualification Toolbox

By David M. Stephon
Elan Pharmaceuticals



Supplier Qualification Toolbox

By David M. Stephon, Elan Pharmaceuticals

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Establishing a Supplier Qualification Program

Section One:
The primary objective of supplier qualification is to assure consistent high quality as demonstrated by predictable conformance to customer requirements.

by
David M. Stephon
Assistant Director, Compliance and Training
Elan Pharmaceuticals

There continues to be considerable interest in the pharmaceutical industry today on the subject of supplier or vendor certification. Supplier qualification programs are intended to be applied to inactive and active components, drug product container and closures, and other packaging materials. There is a critical list of elements that make up a successful vendor certification program. However, certifying or qualifying a vendor or supplier requires different types and levels of effort from various suppliers. It must be recognized, therefore, that circumstances may vary depending on the type of operation, nature of the process involved, and product standard requirements in order that a certain amount of latitude and judgment be used when establishing a supplier qualification program.

Supplier qualification is often based on a total quality management system that assures that a supplier's product is produced, packaged, and shipped under a controlled process that results in consistent conformance to customer requirements. The supplier qualification program is based on the principle of defect prevention, as opposed to defect detection and selection. It supports the concept of quality at the source by ensuring adequate controls and systems are in place the first time around. It substantially reduces or eliminates the need for final quality inspections by the supplier or the customer. Finally, if successfully implemented, supplier qualification should be designed to achieve the desired objectives of product quality improvement, delivery performance improvement, increase in productivity, and cost reduction.

The primary objective of supplier qualification is to assure consistent high quality as demonstrated by predictable conformance to customer requirements. The basic premise of supplier qualification is that when the customer and supplier work together to establish the proper design characteristics, specifications, test criteria, and process controls, the result will be a product that is consistently fit for use and free of defects. While the customer is responsible for assuring the suitability of the item for its particular use or application, it is the supplier's sole responsibility to meet customer requirements.

Supplier qualification programs can be established with existing suppliers, or as part of the initial negotiations with a new supplier. Certification should be considered on the basis of a specific item, process, or manufacturing location, and therefore, would not necessarily include all items purchased from a given supplier or vendor, all items manufactured by the same process or manufacturing line, or all of the supplier's manufacturing sites for that item. Supplier qualification does

not require sole sourcing, but to be successful, requires a long term commitment on the part of both parties. It should allow the supplier to eventually become a low cost, high quality source of pharmaceutical components and packaging materials to the customer. In order for a supplier qualification program to be successful, both the supplier and the customer must have a strong commitment from top management to the operational level.

Supplier qualification programs have often been discussed within the context of the Just-In-Time (JIT) approach to manufacturing and inventory management. While JIT may be a logical goal of supplier qualification, it is not necessarily the primary reason behind the program. However, acceptable quality and reliability of incoming components are crucial to the successful implementation of a JIT program. It is also important to understand that supplier qualification should not be confused with routine supplier selection, reduced testing programs based strictly upon supplier quality history, and statistical quality control assessments. In other words, supplier qualification does not replace existing supplier/customer procedures and relationships, but is an additional tool for achieving the maximum benefits resulting from those relationships.

Definitions

- **Active Pharmaceutical Ingredient** (API): refers to any substance that is intended for use as an active ingredient component in drug products, or a substance that is repackaged or relabeled for drug use. Such chemicals are usually made by chemical synthesis, by processes involving fermentation, or by recovery from natural material.
- **Approved Supplier:** a supplier who has met minimum qualification criteria, and been approved to supply a required item. Full customer inspection and testing would precede use. The supplier provides lot specific certificates of analysis or compliance.
- **Certified Supplier**: An approved supplier who has satisfied all requirements of the customer's supplier qualification program. At this level of qualification, minimal testing (e.g., identification, dimensionals) may only have to be performed before using the item. The supplier provides lot specific certificates of analysis or compliance.
- **Component**: any ingredient intended for use in the manufacture of a drug product, including those that may not appear in the final drug product.
- **Controlled Process**: a documented process run in strict accordance with procedures. One in which sources of variation are identified, monitored and controlled using Statistical Process Control (SPC) and other techniques to ensure that the process produces a product within defined limits.
- **Drug Product**: a finished dosage form, e.g., tablet, capsule, solution, etc. that contains the active drug ingredient(s) generally, but not necessarily, in association with inactive ingredients.
- **Just-In-Time** (JIT): refers to a management philosophy whose goal is to closely link production to current demand by producing only the minimum necessary units in the smallest possible quantities at the latest possible time. JIT aims at achieving this goal by streamlining the production process and increasing flexibility through the reduction of lot sizes, lead times, set-up times, raw material, work-in-progress inventory levels, and waste throughout the manufacturing process.
- **Preferred Supplier**: an approved supplier who is actively participating in the supplier qualification process. A preferred supplier typically has an ongoing excellent quality history. The customer may be operating under a reduced testing program. The supplier provides lot specific certificates of analysis or compliance.
- **Statistical Process Control** (SPC): refers to the methods for improving and controlling a process by using statistical techniques during manufacturing to assure products conform to specifications as they are produced.
- **Vendor or Supplier**: terms used interchangeably to refer to the manufacturer of the purchased item.

Supplier Qualification Implementation

One of the key activities in the successful implementation of a supplier qualification program is the establishment of an effective internal organization for evaluating suppliers within your company. Key members of this group would include personnel from purchasing, Quality Assurance (QA)/compliance, quality control, engineering, operations, and manufacturing. Personnel from research and development and technical services operations can also provide input into the supplier qualification program if the item to be certified is related to a new product introduction.

After the team is formed, often a supplier qualification working group is formed, and directed towards seeking concurrence on objectives, definitions, and the approach that would be communicated to the suppliers. Normally, after completion of this phase, the design, development, and implementation of a formalized program is provided to the suppliers. After this initial assessment of potential benefits of the supplier qualification program, which may include production material requirements, and a list of potential suppliers capable of supporting those requirements, it is usually advantageous to receive confirmation and approval from senior management demonstrating support of the supplier qualification program.

The actual measurement of a company's capability to initiate a supplier qualification program is in identifying the ability of its own manufacturing supply operations to conform to the established criteria the company has defined for itself. The experience of a customer qualifying his own internal process will provide a good indication of some of the difficulties that will be encountered in working with suppliers. This exercise should also result in improvements in the manufacturing operations.

Supplier Classification and Selection

The supplier and customer are both business and quality partners in the supplier qualification process. In order to select a potential supplier for supplier qualification, an initial evaluation of the supplier's capabilities, service performance, and quality history is required. Not all suppliers may qualify for vendor certification. In most cases, several levels of supplier classification may be required in the qualification program. It is important to recognize that not all "approved" suppliers will be certified. Each succeeding classification indicates a higher level of performance and a more consistent quality history for an item.

When an item that has been selected for evaluation by the supplier qualification team has been identified, a meeting is usually held with the supplier to identify capabilities, establish mutually acceptable requirements, and agree on a program to achieve qualification for that item. In order to develop a successful program, adequate communication is required upfront from the customer to ensure that the supplier is aware of and capable of meeting the requirements, and understands and accepts responsibility in the supplier qualification program. Therefore, the supplier and customer teams must mutually agree upon specification and test criteria that verifies intended product usage by the customer. The supplier's process control capabilities must be evaluated, and methods of acceptance or verification must be established.

It is important to conduct joint supplier/customer meetings and site visits to fully comprehend the supplier's process, and the customer's use of the item in manufacturing, and packaging of the final product. This may occur with a visit by the supplier's operational and QA personnel to the customer's plant to observe how the purchased item will be used, its relationship to other parts, and its overall effect on the production process. A site visit and assessment by customer operational and QA personnel to the supplier's plant operations is also necessary to provide an understanding of how the component is manufactured and tested. In addition, the supplier qualification program includes initial quality audits and subsequent due diligence or maintenance quality audits of the supplier by the customer. This ensures that the required level of quality history is maintained as required by the supplier qualification program.

Customer Inspection

After it has been confirmed that a supplier has a controlled process, there usually will be a defined period when both parties evaluate material quality and compare data. This provides the required assurance that the supplier and customer have comparable evaluation ability, and minimizes the potential for future disagreements that are due to test results rather than an atypical product. The customer may also wish to revert to comprehensive evaluation, for example, full testing, to ensure the purchased material or items have remained within the agreed quality specification of acceptance. Supplier qualification provides a strong basis for the application of reduced testing by the customer as allowed under current Good Manufacturing Practice (cGMP) regulations. If the supplier's process is under control, any evaluation by the customer should only add value with respect to changes during shipment. Sections 211.84(a) and (d) of 21 CFR211 do allow for reduced testing after reliability of the supplier's material test results have been established by the customer. But the elimination of incoming material testing by the customer is precluded by 211.84(d)(2) and (3). The customer should perform quality audits of the supplier's process at appropriate intervals. This can also serve as an opportunity to review the entire supplier qualification process and to evaluate its overall success.

Supplier Reporting

For pharmaceutical products, quality is critical. The company's quality unit should routinely audit the quality of the supplier's certificate of analysis for purchased components. Since supplier qualification is a partnership, it is important that both supplier and customer are kept informed of each other's difficulties. The supplier must notify the customer of any atypical situations or process deviations prior to shipping material, so that any additional testing or evaluations may be performed. The supplier should also provide certificates of analysis for every lot of material purchased by the customer, and which is formatted in a manner that is acceptable to the customer. The customer should also provide feedback to the supplier with respect to compliance with specification, performance in use, and delivery service.

Specifications and Process Definition

Another important element in the supplier qualification process is the procedure for handling any changes to the process of the specification that is initiated by the supplier. Any proposed change must be clearly documented under an effective change control management system, with reasons for the change, supporting data, and review by the customer prior to introduction of the change. Some changes may require customer evaluation and even FDA approval before acceptance.

A similar procedure should be in place in the event the customer intends to change the specification. Any proposed changes to the customer's process that could impact on the usability or performance of the supplier's material also require prior review and agreement with the supplier. For example, if the customer was considering replacement of a packaging line, there would be a need to discuss this change with the supplier of the packaging components. Having established a working partnership with the supplier that can manage change will help immensely under these circumstances.

Decertification

Qualification or certification results in a high level of reliance on the supplier by the customer. Reduced incoming inspection, reduced inventories, and higher output are all benefits of this process. Supplier qualification can be lost if the process is found to deviate from the specified documented process. Any deviation from the agreed upon process should be investigated. Depending on the nature and cause of the deviation, and whether the investigation demonstrates the cause was intentional or unintentional, the customer may elect not to requalify the supplier. Any failure by the supplier can therefore have serious consequences, and may require decertification of that supplier for that particular material or class of materials. Depending on the nature of the problem, it may be possible to work with the supplier to reestablish qualification, or the supplier can be relegated to a lesser status, such as "approved" or "preferred."

Benefits of a Supplier Qualification System

The main result of supplier qualification is an assured reduction in quality variability. This provides benefits such as:

- The tighter material specification ranges usually result in higher yields and reduced equipment downtimes for the supplier, thereby providing an opportunity to reduce prices or minimize price increases. This, in turn, has a similar effect on the customer's product quality.
- More consistently compliant batches can result in lower inventories for both supplier and customer. This reduces the cost of maintaining inventory. It also reduces the degree of write off associated with materials that may become unusable because of extended storage, or obsolete because of policy changes.
- Reduced testing by the customer eliminates some testing costs, but more importantly, can make materials available to production more

Figure 1

Quality Assurance Approved Supplier List

Supplier Qualification Program	Output	Measurement
1. Processes/systems for supplier qualification, evaluation	1. Contracts	1. Supplier Performance
2. Written supply agreements	2. Finalized agreements	2. Quality
3. Change notification	3. Supplier partnership established	3. Delivery
4. Performance monitoring	4. Audits	4. Documentation
5. Maintenance	5. Quality Surveillance	5. Service

quickly. This allows further inventory reductions, and also provides benefit when materials are urgently required for unexpected production.

Section Two:

Considerations in Setting Up a Supplier Qualification Program

The knowledge base a particular company has about its incoming materials is often variable, therefore a supplier qualification program is required to be tailored to the company's specific needs. For example, companies that are sponsors of New Drug Applications (NDAs) are likely to work very closely with their critical component suppliers. Quality requirements regarding impurity profiles, degradation studies, and assurance of process validation need to be verified by the pharmaceutical manufacturer before critical biobatches, primary stability, validation, and initial commercial launch batches are manufactured. Conversely, an Over-the-Counter (OTC) pharmaceutical manufacturer may simply purchase compendial grade materials from distributors. In other instances, certain components, excipients, containers, and closures may be custom formulated or designed for a specific product, as opposed to normally acquired stock items. Therefore, depending on the circumstances and product line, a supplier qualification program may be less involved than in other cases.

cGMP standards require that pharmaceutical manufacturers assure through an appropriate program or activity that components meet specifications and quality requirements. The International Organization for Standardization (ISO) 9001 and 9002 standards require manufacturers to select vendors on the basis of their ability to meet purchased specifications.

The FDA's cGMP regulations under 21 CFR 211.84(a) through (e) require a manufacturer to test and approve or reject components, drug product containers and closures. 21 CFR 211.84(d) (2) requires the manufacturer to test each component for conformity with written specifications for purity, strength, and quality, and accept the supplier's report of analysis. 21 CFR 211.84(d) (3) requires the manufacturer to test containers and closures for conformance with all appropriate written procedures, or accept the supplier's report of analysis. However, certain restrictions apply to accepting these reports of analysis.

The restrictions specified in 21 CFR 211 for acceptance of a supplier's report of analysis for components state that the manufacturer must conduct at least one specific identity test on each lot received, and establish the reliability of the supplier's report of analysis through verification of the supplier's test results at appropriate intervals.

Originally, as documented in the Preamble to the 1978 cGMP revision of 21 CFR 211, FDA expected a manufacturer to establish, through its own tests, that supplier reports of analyses on components were reliable. The manufacturer's and supplier's test results are expected to agree within a specified range over a defined period of time. Often, a comparability protocol is used to conduct this comparison testing. Once the reliability of the supplier's data is established, the level of testing conducted by the manufacturer can be reduced. However, a system is required to be in place to ensure continued reliability of test results. This is often accomplished by performing full verification testing annually, or every 10th lot received, whichever occurs first, to ensure continued reliability of test results. It should be noted that the FDA currently does not have a written policy that addresses supplier qualification beyond what is stated in 21 CFR 211.84.

All pharmaceutical components and packaging materials should be included in the supplier qualification program before accepting the supplier's report of analysis as the sole means for accepting materials. The program should include both excipients and APIs, as well as, containers and closures. The type and extent of evaluation of supplier qualification should be dependent on the criticality of the material, previously demonstrated capability of the supplier, and conclusions reached about the supplier following the qualification process. While qualification cannot be achieved without the cooperation and assistance of suppliers, the pharmaceutical manufacturer should make it clear to the supplier that the decision to qualify is based on the requirements of the purchaser.

Evaluation tools for supplier qualification include:

- Supplier document review
- Test methods verification
- On-site cGMP audit
- Corrective Action/Preventive Action (CAPA)
- Notification of acceptance (or qualification) of the supplier.

As part of the supplier qualification program, an evaluation of the supplier's marketing history for a material is sometimes warranted. Review of the regulatory inspection history of the supplier, such

How to Qualify a Supplier

■ **CUSTOMER PREPARATION**

a. Determine whether the supplier is a new supplier to the company, or has a history of supplying materials to other company sites.
b. Determine whether there already exists a qualified supplier for the material.
c. Evaluate the supplier's references and reputation.
d. Customer forms a supplier qualification team that usually includes representation from purchasing, QA/compliance, quality control, engineering, and manufacturing departments.
e. Supplier qualification team reaches agreement on objectives, definition, and approach to the supplier qualification program.
f. A supplier qualification team develops guidelines to facilitate the joint effort between customer and supplier, and identifies suppliers and items to be pursued with initial priority.
g. Customer supplier qualification team obtains complete support from senior management.
h. Define the supplier's operation and capacity.

■ **PRESENTATION**

a. Customer meets with supplier to explain the supplier qualification program.
b. Customer engages the supplier to work together within a partnership to achieve qualification of specific processes and materials.

■ **ACCEPTANCE**

a. Supplier formally communicates to customer the supplier's commitment to work together to achieve supplier qualification.
b. Supplier and customer commit to required human and financial resources to ensure the supplier qualification program works correctly.

■ **SUPPLIER QUALIFICATION TEAM**

a. Supplier forms its supplier qualification team. This team typically consists of the plant manager, operations, processing, engineering, maintenance, Quality Assurance (QA), and quality control technical staff.

■ **ORIENTATION PROGRAM**

a. Meetings are jointly conducted between supplier and customer.
b. Meetings establish communication channels between partners, quality requirements and specifications are clarified and explained, and manufacturing processes are jointly understood by both parties.

■ **ASSESSMENT PERIOD**

a. Conduct verification testing on a defined set of lots of the supplier's material.
b. Generate a qualification protocol to evaluate "use testing" of the component in the final dosage form.
c. Conduct a cGMP audit or alternative assessment tool, such as a quality audit questionnaire.

■ **NOTIFICATION**

a. Provide formal notification to the supplier that the material being sourced has been qualified.

■ **MAINTENANCE PERIOD**

a. Periodic repeat testing.
b. Decertification.

as an FD483, or Warning Letters should also be conducted. For critical materials, document review should extend to product-specific flow charts, validation protocols and reports, summaries of conformance to test specifications, quality systems, change control, and investigational procedures.

Product specifications, standards, required equipment, and test methods must be evaluated to assure the capability exists, either by the pharmaceutical manufacturer or qualified contract laboratory, in order to conduct the verification testing. Generally, when a material is purported to comply with compendia requirements, or when basic testing or an inspection procedure is used, the identification and testing procedures can be applied using minimal comparative testing. Samples of the supplier's material and corresponding test results can be requested from the supplier. The conduct of on-site cGMP audits by the pharmaceutical manufacturer or qualified third party consultant provides an opportunity to review the supplier's facility, equipment, and operations. Alternatively, a quality audit questionnaire can be used to obtain information on the supplier's operations.

Section Three:

Your Company's Name	**Standard Operating Procedure**	*Effective Date:*
Document Number:	*Title:* Supplier Qualification Program	*Page:* 1 of 4

1. PURPOSE

1.1. To provide a consistent procedure for qualifying approved suppliers in order to establish a reduced testing program for components, containers, and closures in accordance with 21 CFR 211.84.

2. SCOPE

2.1. This SOP is followed when establishing a component, container, or closure supplier as an approved supplier.

Note: The FDA cGMP regulations under 21 CFR 211.84 states "each lot of components, drug product containers, and closures shall be withheld from use until the lot has been sampled, tested, or examined, as appropriate, and released for use by the QC unit." This section of the regulations goes on to define the specifics of such testing or examination. However, the regulations do allow for relief of full testing under CFR 211.84(d)(2) and (3) by stating that in lieu of such testing by the manufacturer, a report of analysis or certificate of testing may be accepted from the suppliers of these materials, provided that at least some identification test is performed by the manufacturer, and the manufacturer establishes the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals. In addition, compliance to cGMP regulations needs to be established with the vendor by the manufacturer's Quality Assurance (QA) department. All of these activities constitute the approved vendor certification program.

3. RESPONSIBILITY

3.1. Quality Control (QC) determines reliability of component, container, or closure supplier test results.

3.2. Quality or compliance department conducts cGMP audits of component, container, or closure supplier, and determines the acceptability of the supplier as qualifying as an approved supplier.

4. DEFINITIONS

4.1. Container: That entity which holds the article and is, or may be, in direct contact with the article.

4.2. Closure: That part of the container system that is intended to contribute to the preservation of the quality, purity, strength, and identity of the article housed in the container.

4.3. Component: Any ingredient (active or inactive) intended for use in the manufacture of a drug product that may appear in such a drug product.

4.4. Supplier: The manufacturer of the purchased item. Also known as the vendor.

4.5. Approved Supplier: A supplier that has satisfied the minimum qualification criteria of the supplier qualification program, and has been approved to supply a required raw material. Requirements to meet a status of approved supplier include undergoing a successful initial quality audit, and/or completion of a quality audit questionnaire. Full release testing is required for all materials sourced from approved suppliers.

4.6. Preferred Supplier: An approved supplier that is actively participating in the supplier qualification process. Requirements to meet the status of a preferred supplier include an established acceptable quality audit history, and demonstration that all received material lots to date, consisting of at least three (3) consecutive lots, have been confirmed as meeting specifications based on supplier verification testing by the manufacturer's QC department.

Your Company's Name	**Standard Operating Procedure**	*Effective Date:*
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Full release testing is required from all materials received from preferred suppliers.

4.7. Certified Supplier: A preferred supplier that has satisfied all requirements of the supplier qualification program. Requirements to meet the status of certified supplier include an established acceptable quality audit history, and demonstration that all received material lots to date, consisting of at least an additional two (2) consecutive lots, have been confirmed as meeting specification based on verification testing by the manufacturer's QC department. Reduced testing, consisting of at least one (1) specific identification test, and receipt and review of the supplier report of analysis may be used to release the material for use.

5. PROCEDURE

5.1. Determine the need to establish the component, container, or closure supplier in the Supplier Qualification Program (Production QC).

5.2. Notify QA/compliance to determine approved supplier qualification requirements (Production, QC).

5.3. QA/compliance schedules and conducts an initial cGMP compliance audit of the selected supplier. This audit may also include or be substituted by the use of a supplier completed quality audit questionnaire, depending on the criticality (e.g., early versus late clinical phase use) of the component, container, or closure usage.

5.4. If the supplier is determined to meet cGMP requirements as established by QA/compliance, an initial status of approved supplier is granted by QA/compliance.

5.5. Based on the frequency of material use from the approved supplier, the status of the supplier may be upgraded to preferred supplier by establishing a verification testing agreement between the supplier and manufacturer for each material type and grade being sourced from that supplier. This agreement outlines a specified number of lots to be jointly tested by the QC department and supplier, where the number is required to be a minimum of three (3) consecutive lots. *Note: If an agreement to a verification testing protocol is not feasible due to the supplier's unwillingness to enter into such an agreement based on the manufacturer's infrequent use of the vendor, or for any other business reasons as communicated by the vendor, the manufacturer reserves the right to establish the reliability of the supplier's test results on three (3) designated incoming lots of the material, and tested against the supplier's tests, and/or manufacturer established quality standards.*

5.6. If the test results generated by the QC department are determined to be satisfactory, QA/compliance reviews the supplier's audit status and the release results, and compares to the QC department's test results. This comparison determines if the supplier qualifies for a preferred vendor status.

5.7. If a vendor is determined to be eligible for certified supplier status, an additional two (2) consecutive lots are tested by the QC department for verification testing.

5.8. If the test results generated by the QC department are determined to be satisfactory, QA/compliance reviews the supplier's audit status, and the supplier release results, and compares to the QC test results. This comparison determines if the supplier qualifies for a certified vendor status.

5.9. For approved, preferred, or certified suppliers, regulatory documentation establishes a vendor file for the supplier that contains results of the supplier and QC verification testing, and a copy of audit report(s) of the supplier conducted by QA/compliance.

5.10. The current approved, preferred, or certified supplier rating is entered into the QA/compliance approved supplier list. Refer to *Figure 1*.

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Classification status of an approved supplier is maintained by continued demonstrated ability of the supplier to meet required quality standards as determined by the QA/compliance audit program. Classification status for preferred or certified suppliers is granted by QA/Compliance for a period not to exceed two (2) years with exceptions to exceed the two (2) year cycle for re-certification status listed under 7.12 - 7.13.

5.11. QC determines the selection of the appropriate tests required to accept material from the supplier under the reduced testing program. Selection is based on test criteria that can detect potential quality changes of material during handling and transportation from the supplier to the manufacturer, and that includes, at a minimum, a suitable identity test.

5.12. If one (1) or more lots are rejected by QC during the reduced testing program period established with a preferred or certified supplier within the granted certification period, an investigation is conducted to determine cause and to establish corrective action.

5.13. Following the successful investigation by QC and corrective action by the supplier, a successful re-audit of the supplier and verification of supplier test results as described above is required to re-establish the supplier as a preferred or certified supplier by QA/compliance.

5.14. Biennial (every 2 years) re-certification of a preferred or certified supplier is required in order to maintain the supplier on the approved vendor list.

5.15. Biennial (every 2 years) re-certification (surveillance of a current approved supplier) occurs by successful completion of an annual QA/compliance cGMP audit, full testing, and verification to vendor results by QC on a minimum of one (1) lot.

6. RECORDS

6.1. Exhibit A: QA/compliance approved supplier list. Regulatory documentation assigns Supplier File (SF) numbers. SF numbers are assigned sequentially as SF-# beginning with SF-1 and continuing indefinitely.

7. RECORD DISTRIBUTION

7.1. Supplier files are maintained by regulatory documentation.

7.2. QA/compliance approved supplier list is maintained by regulatory documentation.

8. REVISION LOG

Revision Number	Revision Date	Section(s)	Description
00		NA	Original Issue

9. APPROVALS

Written By: _____ Date: _____

Reviewed By: _____ Date: _____

Approved By: _____ Date: _____

Quality Unit

Your Company's Name	Standard Operating Procedure	Effective Date:
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EXHIBIT A

APPROVED SUPPLIER LIST

Quality Assurance (QA) Approved Vendor List

Material	Supplier Name/ Location	Status	Date Classification Granted	Supplier File Number
Poloxamer, NF	ABC Excipients Anywhere, USA	Approved	01-Apr-2002	SF-1

Section Four:
Supplier Quality Auditing

A quality audit determines whether a new or existing supplier is suitable for supplying components to the specification required by the customer, or whether an existing supplier is continuing to meet the specification required. Oversights at this stage can have serious implications, both from a quality and financial standpoint. It is therefore essential that continuous quality audits be performed as part of the supplier qualification program.

Quality Auditor

Since there is considerable complexity in quality auditing, various types of industry involved, and a limited time period for performing the audit, the quality auditor must have the appropriate requirements, training background, and experience to perform the audit. Some required attributes include:

- The auditor must be a realistic, practical person capable of quickly understanding process details, and practical problems encountered by the supplier. This will ensure that unrealistic demands are not placed upon the supplier by the auditor.
- The auditor must be capable of communicating with staff at all levels, from the production supervisor to the laboratory personnel. This ability is necessary for the auditor to fully access the quality system of the supplier.
- The auditor must be very observant, and be prepared to ask questions that provide background information efficiently, and be able to look behind areas and bypassed equipment during the plant tour.
- The auditor should have extensive experience with the intended use of the components or packaging materials, and in particular, potential quality problems and standards that may be encountered during use.
- The auditor should have full awareness of the GMP requirements for component manufacture and usage. The auditor should also be aware of the regulatory requirements and the particular country requirements in which the final product will be sold using the sourced component or packaging material.
- The auditor should have experience of the component or packaging material manufacturing process prior to conducting the supplier quality audit.
- The auditor can usually acquire knowledge of component and packaging material processing and quality requirements by touring companies involved in manufacturing similar materials. By doing this, the auditor obtains experience for the required GMP standard for that industry. Not having this experience can often result in an unrealistic standard being requested of the supplier.

Auditing

All suppliers should be quality audited at least once prior to initial use, and then on a reasonable periodic basis as required under the supplier qualification program. The quality auditor must prepare in advance of the audit. This usually involves some background information on the company to determine the main business the company is involved in. It is also important to determine whether the company normally supplies components, packaging materials, or other materials to the pharmaceutical industry. A company that has never supplied a customer with strict GMP standards may require re-educating from management down to the operations level. Unless there is an alternative supplier, this is usually a monumental task and requires extra resources of the customer. It is also important to determine if non-standard production is being requested. In other words, the supplier is providing the customer with very small quantities of the material when they usually produce very large quantities using dedicated lines. This can sometimes highlight several problems for the quality auditor to follow up during the audit. This includes:

- Line changeover (clearance) procedures will require special attention, particularly with respect to clean-down and reconciliation.
- A forecast production system may be operating to produce the materials for the customer. In other words, six (6) months or a year's predicted process output would be produced at a time to minimize costs; for example, production of molded bottles using special glass. This system would require the supplier to store stocks for a considerable amount of time. Under these circumstances, the packaging and warehouse would need special attention because of the possibility of pest contamination or material deterioration during prolonged storage.

Based on this, auditor oversight can sometimes occur if a set auditing sequence (e.g., checklist) is not followed, leading to important areas being missed. It usually best to start at the beginning, i.e., raw material storage area, and follow through the process in the manufacturing sequence to the final dispatch to the customer. In this way, all aspects of GMP requirements at each stage can be reviewed.

GMP Requirements For Raw Material Storage

There can be a wide variety of raw materials, considering the many different types of components and packaging materials that are used by pharmaceutical companies. However, one of the most important aspects of raw materials is their storage prior to use. This is an important area to consider in that raw materials must be stored in a way to minimize chemical and physical deterioration, and also to prevent contamination prior to use. Special storage conditions may be required for some raw materials. The GMP considerations would be:

❶ A building of sound, solid construction and design to minimize vermin infestation (e.g., birds, insects, rodents). Usually the large access doorway to the storage area or warehouse is the common entry point for such infestation. Therefore, ensuring this area is kept closed at all times is an important discussion to have during the supplier quality audit. In addition, regular inspections and control measures should be carried out, using a written pest control program that applies approved pesticides.

❷ The building should preferably have no windows, as sunlight can deteriorate, discolor, or fade materials.

❸ The building should have a sealed concrete floor or similar material that minimizes dust generation from fork-lift trucks and related warehouse equipment.

❹ It is important to ensure that open drains are not present in the warehouse. These drains are potential sources of bacteriological contamination to stored raw materials.

❺ The warehouse should be monitored for both temperature and humidity, and have adequate probes located where materials are actually stored (near ceiling, near floor), not just at eye level. Adequate heating and air conditioning may be necessary to prevent deterioration of some raw materials.

❻ Adequate segregation of different materials to prevent possible mix-ups, damage, or contamination should be part of the warehouse layout. Liquids should be stored at ground level, with an entrapment in the event of spillage. No items should be stored in direct contact with the floor of the warehouse. Materials should

not be stored on wooden pallets as these represent a source of contamination. Rather, non-porous, easily cleaned plastic pallets should be used for material storage. High rack storage should be used to make the most efficient use of space available, and to prevent damage of materials from placing one pallet on top of another. An overcrowded storage area can create physical damage to goods, inhibit proper cleaning of the warehouse, and also make access difficult.

❼ It is also important to ensure there is an organized storage and stock control system to ensure correct stock rotation (i.e., First In First Out [FIFO] practice). Each raw material must be reassessed if not used within a defined period of time, as determined by QA procedures.

❽ Status labeling and quarantine areas should be set aside for storage of materials scheduled for testing. There should also be caged material reject areas. It is important to determine what type and frequency of rejects the supplier is having with its own suppliers, and more importantly, what actions have been taken to prevent recurrence. Physical separation and status labeling should be checked for a selected set of materials in the warehouse against actual test results and release records. If a computer control system (e.g., Enterprise Resource Planning [ERP]) is in use instead of status labeling, validation evidence should be provided that the automated system has the ability to adequately distinguish between the current material status or bar code (quarantine, approved, rejected, etc.).

❾ It is important to ensure that documentation exists for all raw materials in the warehouse. All raw materials should be received from the supplier with certificate of analysis or compliance, and also be sampled and tested upon receipt. It should be verified that sampling is performed in a dedicated area (cleanroom, sampling, and weigh booth).

GMP Requirement for the Formulating Area

The quality auditor must also be aware of GMP controls for the formulating area when evaluating a supplier's operations. Areas to review include:

❶ Verify that a dedicated clean area is available for weighing and mixing materials. Room use logbooks, room status labeling, and room cleaning procedures should be reviewed.

❷ Authorized formulation procedures should be available for all stages of compounding and processing.

❸ It is important to verify that only one formulation component is weighed and mixed at a time in any one area in order to prevent mix-ups and cross-contamination.

❹ Labeling of staged materials and processing equipment should be verified. Each weighing operation and addition to a batch should be verified by another trained operator or supervisor. All operations carried out to produce the batch should be clearly documented on the batch record.

❺ Evaluate if the supplier is using automated equipment to execute steps in the manufacturing process, such as Programmable Logic Controllers (PLC) and Supervisory Control and Data Acquisition (SCADA) systems. Adequate qualification and validation of these systems should be verified.

❻ Weighing and processing equipment should be under a qualification, calibration, and preventative maintenance program. Calibration standards should be traceable to recognized government bodies. Equipment should be challenged over its entire operating range, and all records should be maintained.

❼ Each operator and supervisor should have the proper training, education, and experience, including skills and GMP training, to allow them to carry out their assigned job duties.

GMP Requirements for the Production of Components and Packaging Materials

Whether inactive or active components, printed labeling materials, molded closures, bottles, vials, capsule shells, cardboard shippers, etc. are involved, there are several rules that need to be followed to ensure that quality is maintained. These include:

❶ The quality auditor should verify that each piece of processing equipment or machines are separated by a barrier, or at least sufficient space is allowed to ensure that neither materials or staff overlap of operations occurs. In most cases, there should be a separate room for each type of process equipment. This allows cross-contamination to be con-

trolled between materials.

❷ Operators assigned to one process line or equipment train should not be observed moving from one room to another.

❸ Prior to the start of production, a check should be performed to ensure all batch record requirements are available and ready for use. The equipment and the area must be cleaned according to approved procedures, logbooks entry requirements, and updating of status tags. The equipment and room must be completely free from materials used or produced in the room and equipment previously. For example, the correct molds should be fitted to the molding machine with the correct batch or polymer mix, correct print text, and colors for a packaging material operation.

❹ Equipment operators, supervisors, QA staff, and engineers must have complete training records demonstrating skills and GMP training requirements have been satisfied. Special attention should be paid to situations where new operators are assigned to a production line without training.

❺ An in-process control system should be operated on each piece of production equipment or production line. This usually involves regular monitoring by QA/compliance personnel (e.g., pouch integrity checks, dimensional checks, text verification) following standard operating procedures (SOPs). All checks should be recorded with quantity, time of sampling, and results. It is important to have representative sampling during the operation (e.g., beginning, middle, and end).

❻ The output from each process line should be placed into clearly labeled containers or bins. The labels for these containers must be prepared in a secure area and be accurately reconciled. The label should state material name, reference code, batch number, quantity, date produced, shift, and identification of operator.

❼ With primary components, special packaging may be required to minimize contamination during transportation (i.e., non-fiber shedding materials, double bagging, packaging under clean conditions.) Such precautions can minimize cleaning problems by the customer.

❽ Each batch produced from an equipment line must be quarantined until released by QC.

Additional Audit Considerations

The quality auditor should verify that the finished product storage area has the same controls as those used for the warehouse operation for the storage of incoming starting materials. Each material order should be maintained separately for each batch on a separate pallet. Rack storage should be used. Loaded pallets should not be stacked on top of one another unless the component packaging has been designed to accommodate the weight.

…auditor oversight can sometimes occur if a set auditing sequence (e.g., checklist) is not followed, leading to important areas being missed.

When the audit has been completed, the auditor should prepare an audit report that provides an overall summary and audit rating for the supplier. Audit observations should be classified, depending on their significance. A copy of the audit report should be forwarded to the supplier requesting a response with a defined timeline. The follow up to this audit report should be regular communication and cooperation with the supplier to resolve any GMP problems observed. The auditor should also provide recommendations that will help the supplier correct GMP deficiencies as efficiently as possible. It is the decision of the quality auditor as to whether a supplier is acceptable, or if GMP improvements are necessary before acceptance. An official list of all approved suppliers should be maintained by the pharmaceutical company. This is usually maintained by the QA/compliance department. Each approved supplier should be audited at regular intervals to ensure that the quality standards have been maintained. This is usually performed every one to two years, or whenever serious problems are encountered.

Problems Encountered By Auditors

Sometimes quality audits do not go as planned. The following are some situations that may be encountered by quality auditors during supplier audits:

❶ Pharmaceutical company requirements are sometimes insignificant compared to a supplier's other customers. Therefore, suppliers may not be prepared to improve their standards to suit the pharmaceutical industry. This situation usually occurs when there are no other suppliers of a particular item. Until an alternative supplier becomes available, the quality will have to be built into the product by the pharmaceutical company after procurement from the supplier (e.g., extra washing, 100% inspection). This situation is far from ideal, but, provided it is dealt with correctly, the customer's extra processing and testing requirements will result in a satisfactory component or packaging material.

❷ Suppliers sometimes cannot financially afford to bring their manufacturing premises/processes to the required standard that the customer is requesting. Under these circumstances, if this represents the one supplier that can supply a critical component or packaging material, sometimes the pharmaceutical company may elect to produce the component or packaging material under their own operations.

❸ Suppliers not following the manufacturing process through in logical order during the audit. This can cause confusion for the auditor, who may miss an important area to inspect. A likely situation for this to occur is when the next stage of the process is at the other side of the factory, and a later stage is nearer. In this situation, it is best to insist on following the process in logical order, as this gives an indication as to how the supplier's operations are organized.

❹ Suppliers trying to keep auditors from problem areas in their operations, by spending too much time in areas that are compliant or not critical. This ensures there is insufficient time to review and tour the lower standard areas of the operation. This situation can be alleviated by using a written audit plan where a strict timetable is adhered to.

❺ Spending too much time around the conference table or at lunch, leaving less time to be performing the quality audit. This can be minimized by following a very strict audit plan with predefined timetables to execute every section of an audit.

Conclusion

It is important to have a good working relationship with a supplier, and a carefully constructed purchasing policy will help to achieve this goal. A system of single or multiple sourcing of components and packaging materials can have a significant effect on the final quality of the purchased materials. A supplier must be capable of current and future production requirements. If a supplier attempts to produce at a rate that exceeds equipment or operator capability, this inevitably leads to quality problems. It is also necessary to ensure that a selected supplier is commercially viable, as a company suddenly filing bankruptcy may cause a serious component shortage problem for the customer. This is an instance where having more than one approved supplier is an advantage. This requires an extra resource investment involved in auditing, and maintaining more than one supplier for a selected component or packaging material, and often increases the risk of quality problems. In these cases, where multiple supplier sourcing is used, a good communication network is essential in minimizing quality problems with the suppliers. ❑

Section Five:

Supplier Quality Audit Questionnaire

Completed by Quality Compliance

Contractor/Vendor/Supplier Information

Corporate Headquarters _____
Full Street Address: _____

Telephone Number: _____
Facsimile Number: _____

Manufacturing Site
(if different from above)
Full Street Address: _____
_____
_____

Telephone Number: _____
Facsimile Number: _____

Materials that will be purchased/service(s) that will be provided:

_____

To be Completed by Contractor, Supplier, or Vendor

1. In what year was the company established?
2. Who owns the company?
3. Please provide an organizational chart showing the reporting structure of the company and attach to the questionnaire.
4. List the name and address of the parent organization.
5. Is there a registered U.S. Drug Master File (DMF)? If yes, provide the DMF number and the name of the regulatory agency(s) that the DMF is registered with.
6. How many work shifts operate at the manufacturing site?
7. How many employees work at this manufacturing site?

   Full-time _____ Temporary _____ Part-time _____ Contract _____
8. What is the size of the facility?
   Please attach a copy of the plant layout to this questionnaire.
9. Have the Food and Drug Administration (FDA) Department of Health and Human Services (DHHS), Health Products and Food Branch [Health Canada's Regulatory Branch] (HPB), the European Agency for the Evaluation of Medicinal Products (EMEA), any other responsible regulatory authority, or any other of your customers inspected this site within the past ten (10) years? If yes, please provide dates of inspection and inspection details (e.g., inspectional observations, Warning Letters, etc.) and attach to questionnaire.
10. Please provide information on contact personnel:

	Name	*Phone/FAX*
Plant Manager	_____	_____
QA/QC Manager	_____	_____
Production Manager	_____	_____

11. Is there an internal quality audit program that covers all areas of the operation to verify that procedures and policies are being followed, and determines the effectiveness of the quality systems?
12. Are internal audits documented?
13. Are corrective actions documented?
14. Please describe your procedure for handling and conducting product complaint investigations? Does the quality unit approve all complaint investigations?
15. Are items manufactured in isolated areas using dedicated equipment?
16. If equipment is not dedicated, what other types of materials are manufactured in the same equipment?
17. Are all pieces of equipment used in the manufacturing process cleaned? If so, does the validated cleaning process include the use of surface swabs? Have methods for sampling been validated and approved by your Quality Unit? Are records for cleaning maintained?
18. How does your firm address minor equipment cleaning (e.g., spatulas, transfer hosing, etc.)?
19. Have time limitations been established for the period between when an equipment piece has been cleaned versus the requirement to re-clean before subsequent use?
20. Please describe the system and procedures for documenting cleaning and use of the equipment (equipment log).
21. Are there data to show that cleaning procedures for non-dedicated equipment are adequate to remove previous materials?
22. Have cleaning procedures been validated?
23. Is equipment constructed so that product-contact surfaces are not reactive, additive, adsorptive, and will not adversely affect the product?
24. Is product exposure to, or contamination with, lubricants or coolants possible? Are these materials food grade?
25. Are there adequate space and environmental controls to ensure product integrity, and to preclude mix-ups and cross-contamination, especially in drying, milling, blending, and packaging operations?
26. Are exposed materials protected from overhead contamination?
27. Are production areas that present potential contamination properly controlled and equipped with exhaust or other appropriate systems?
28. Is air recirculated to areas where the product is exposed? Is it filtered and controlled to eliminate cross-contamination? Are such filters periodically checked and replaced? Is this activity documented?
29. Please describe the general procedure for maintaining the facility in a clean, sanitary, and orderly manner?
30. Are there adequate procedures for sanitation and cleaning of facilities? Please briefly describe.
31. If raw materials or intermediates are stored in silos, tanks, or other large containers, are vents adequately protected to prevent entry of water, birds, and insects?
32. Are any of the following produced at the same location, or near the same location, as materials that will be, or are currently being purchased by our firm? If yes to any category, please specify the type.

_____ Beta-lactams (penicillin/cephalosporin)
_____ Steroids
_____ Pesticides/Herbicides
_____ Other potent substances
_____ Cytotoxics
_____ Agrochemicals
_____ Biologicals

33. If yes was answered to question number nine, explain how cross-contamination potentials are minimized.
34. Which job function is responsible for approving SOPs?
35. Are there clearly written job descriptions?
36. Is the quality unit's authority and responsibility clearly defined in writing?
37. Does the quality unit have independent authority to approve and reject procedures, specifications, and process changes?
38. Does the quality unit have the authority to ensure that manufacturing and testing records are reviewed before batches are released for sale?
39. Does the quality unit review and approve failure investigations and complaints?
40. Please describe the program to qualify suppliers of raw materials, components, and services that might affect quality, and verify that they have the capability to consistently meet agreed upon requirements.
41. Does the supplier program include periodic audits (or other verification techniques) of suppliers?
42. Please describe the program used to evaluate vendors (service providers, e.g., metrology).
43. Is a list maintained of approved sources for raw materials employed in the manufacturing process? Are incoming materials checked against this list?
44. Is there an adequate system to assure that suppliers and subcontractors notify the company of significant changes?
45. Are containers and equipment clearly labeled to identify the contents and, if appropriate, the stage of manufacture?
46. How are changes to the manufacturing process authorized? Does the quality unit approve all changes?
47. Are reworks/reprocessing procedures approved by the quality unit? Are reprocess procedures validated?
48. How is batch/lot reprocessing/rework authorized?
49. Describe your firm's batch/lot numbering system?
50. Please attach a general process flow diagram that describes the manufacture of the material.
51. Explain how batch/lot uniformity (homogeneity) is assured. Is the process validated? Are the sampling procedures validated? Are in-process tests utilized and established specifications in effect?
52. Is the manufacturing process validated for this material? If yes, is the validation prospective, concurrent, or retrospective? Are validation reports available and approved by the quality unit? If not, what is the target date for completion of the process validation?
53. Is there a process flow diagram for the manufacture of the product? If so, please attach to questionnaire.
54. Are subcontractors used for any part, or all, of the manufacturing process, e.g., fermentation step or extraction step? For control testing, e.g., water testing, microbiological testing? If yes, please explain. Please provide the name and address of any subcontractor(s).
    If yes: _____
55. Is there a written pest control program? Are records of pest control maintained? Are rodenticides and pesticides selected and approved for use in the facility?
56. Is there a procedure for the receiving, reviewing, handling, storage, issuance, and accountability of pre-printed labels?

57. If labels are printed as needed, is there a system to verify the accuracy of the labels?
58. Is a copy of the product label retained in the batch record?
59. Is there an SOP for label reconciliation?
60. Does the final product label contain adequate information to identify the contents, quantity, lot number, and manufacturer?
61. Who within your organization will notify our firm of such an inspection that impacts raw materials, processes, and active ingredients?

Name: _____
Title: _____
Phone/Fax Number: _____

62. Who within your organization will handle any complaints regarding the material(s) of concern for Elan Pharmaceuticals?

Name: _____
Title: _____
Phone/FAX Number: _____

63. Please describe your site's environmental monitoring program, especially at key points of ingredient and material exposure (e.g., sampling, weighing, compounding, blending, etc.).
64. Please briefly explain your site's monitoring programs for water, steam, and/or air/gas systems.
65. For equipment located outside a controlled environment (e.g., reactor, centrifuge, dryer), is a closed system used? Please describe.
66. What grade of water is used for processing? Potable, purified, Water-for-Injection (WFI) or other? Please specify: _____
67. Is the water system, that is used in the manufacturing process and/or used for cleaning equipment for which there is product contact, validated and routinely monitored against applicable requirements? If not, what is your target date for completion of the water system validation?
68. Is feed water coming into the plant periodically monitored for chemical and microbial quality? How is this monitored; in-house testing or municipality testing reports?
69. Are there chemical and microbial quality standards and action limits established for process water? Are these specifications based on an environmental monitoring program?
70. If chemical or microbial quality standards are exceeded, is the cause investigated, problem corrected, and impact on the contamination of products evaluated? Please briefly describe.
71. Please describe your site's on-going equipment and instrument qualification, calibration, and preventive maintenance program. Are calibration records maintained for each piece of equipment or instrument? Is there a procedure for qualifying new or significantly changed production and laboratory equipment?
72. Please describe your cGMP employee training program. Is the program in writing? How often is GMP training conducted?
73. Is GMP training conducted by qualified individuals?
74. Are job-specific training requirements clearly defined?
75. Is GMP training conducted for new and temporary employees?
76. Are training and qualifications documented for each employee?
77. Please explain how employee proficiency is monitored and measured?

78. Is there a FIFO system for stock rotation? Are there separate areas defined for storage of materials on receipt and after testing?
79. Are there temperature and relative humidity controls in place in the warehouse?
80. What precautions are taken to prevent contamination of materials during dispensing?
81. Are reserve samples of raw materials retained?
82. Is there a written sampling plan for all raw materials used in all products?
83. Are any raw materials that are used in products accepted on the basis of the manufacturer's certificate of analysis only? If yes, explain your company's reduced testing program for raw materials.
84. Is the quality unit responsible for the approval and/or release of raw materials, in-process materials, and finished product? If not, please describe this responsibility in your company.
85. Is the quality unit responsible for the writing of investigative reports? Investigative reports are written as a result of a planned or unplanned manufacturing change to demonstrate that the quality of the material or product has not been compromised due to a variation in the production process. If not, who has that responsibility?
86. Are investigative reports extended to other batches/lots of the same product?
87. Is there a procedure for determining the fate of final product that fails to meet specifications (e.g., reprocessing, downgrading to a lesser grade, release with agreement from customer, destruction)?
88. Are quarantine procedures established with designated areas for labeling of released (approved) lots of materials?
89. Briefly describe at which stages in the production process, yield calculations and materials reconciliation are made, and how.
90. Are all release testing methods validated? Are methods validated according to current regulatory and compendial guidelines? Does the method address all anticipated impurities, and is it based on the synthetic process?
91. Does a sampling procedure exist for raw materials, in-process products, and final product? Is the procedure validated?
92. Does your firm have change control procedures for the manufacturing process, equipment, or systems? Does a system exist for the review and approval of changes to the manufacturing process? Are changes evaluated for impact on validated cleaning or manufacturing procedures? Are your customers notified of changes prior to the implementation?
93. Does your firm conduct stability studies for raw materials, in-process materials, or final product? Is there a written stability program? Are stability samples stored in the final product container? If so, what are the time points and stations listed in the stability protocol?
94. Does your firm generate impurity profile data? This data would include in part, those impurities found due to heat stress, high and low humidity, high and low pH, exposure to visible and/or UV light, exposure to oxygen, in addition to those impurities found as a result of the manufacturing process and/or carryover from raw materials. If not, why not? What are your plans to start these studies?
95. What levels of process impurities and degradants are typically contained in material? What is the impurity profile and specifications?
96. Are tests for specific residual solvents used on a routine basis? What solvents are controlled? What levels are typically found?
97. Provide details of the method used to detect residual solvents.

98. Have stability indicating methods been developed, and are they employed on a routine basis as part of the stability testing program?
99. Have time limitations been established for the period between when a manufacturing area has been cleaned, versus the requirement to re-clean before subsequent use?
100. Does your firm have a procedure for re-testing a sample that has failed specification? If so, please explain.
101. How many employees are in the control testing laboratory?
102. To whom does the laboratory manager report?
103. List the major equipment pieces in the control testing laboratory?
104. Is microbial limit testing performed on the finished product?
105. Are retains of the final product maintained? If so, what quantity?
106. Are expiration dates assigned to products manufactured by your firm? If so, how are these dates determined?
107. If special storage conditions are necessary, based on the results of stability testing, are they specified on the label?
108. Please attach a copy of your firm's QA/Compliance organizational chart.
109. Attach a copy of the Certificate of Analysis for one batch of product.
110. Please describe, or attach a copy of, your procedure for how your firm (will) communicates important information to Elan Pharmaceuticals. This information would include: Results of regulatory inspections regarding materials or products purchased by Elan Pharmaceuticals, planned significant process changes (these changes might require a regulatory filing update, or the changes might affect some physical characteristic of the product), changes in the product release testing procedures, reporting of out-of-specification test results, and/or stability data for materials or products purchased from your company. Which person in your firm is responsible for communicating this information?

    Name: _____

    Title: _____

    Phone/Fax: _____

111. Please state the name, address, and contact information for the individual that completed this questionnaire:

    Name: _____

    Title: _____

    Phone/Fax: _____

Date the Supplier Quality Audit Questionnaire was completed: _____

Thank you for completing this Supplier Quality Audit Questionnaire. Please return the completed form to:

Quality Compliance Department

Your Company Name

Section Six:

Supplier Quality Audit Checklist: Active Pharmaceutical Ingredients

Company Name: _____ Date: _____
Company Address: _____
Facility/Site: _____
Active Component: _____

	Yes	No	Comment
Background			
1. Has the FDA Establishment Inspection Report (EIR) from the last FDA inspection been reviewed, and have all areas of non-compliance been addressed?			
2. Have the inspection reports from local, national, or other regulatory agencies been reviewed? Have all areas of non-conformance been addressed?			
3. Is there a list of products (Active Pharmaceutical Ingredients [APIs], intermediates) manufactured at the plant?			
Quality Unit Responsibility			
1. Is the quality unit independent of production? Does it fulfill both Quality Assurance (QA) and Quality Control (QC) responsibilities?			
2. Are quality-related activities recorded at the time they are performed?			
3. Are discrepancies that occurred during manufacturing, packaging, and testing (including Out-of-Specification (OOS) results) properly investigated? Are corrective actions taken and documented?			
a. Is there a procedure that describes failure investigations?			
b. Is there a procedure that describes the acceptance criteria for decisions covering OOS results and rationale for retesting?			
c. Are all investigations documented and reviewed within specific timeframes?			
d. Does the investigation include an evaluation of the impact of the results on related systems?			
e. When a cause is identified, is there a plan established for corrective action and follow-up?			
4. Does the quality unit approve all raw materials before they are used in batches?			
a. Are there appropriate systems in place for release under quarantine, as needed?			
5. Are there procedures for notifying management in a timely manner of regulatory inspections, serious GMP deficiencies, product defects, recalls, and complaints?			
6. Are all records reviewed for completeness, accuracy, proper recording of information and legibility? Are there adequate cross-references to associated documents, as applicable?			
7. Roles and Responsibilities of the Quality Unit			
a. Have written procedures been established that designate what personnel have authorization to release intermediates and finished APIs?			
b. Has a system been established to release or reject raw materials, intermediates, packaging, and labeling materials?			
c. Does the quality unit review include completed batch production records and laboratory control records for critical process steps prior to release of the API for distribution?			
d. Does the quality unit review and approve specifications and master production instructions?			

Supplier Quality Audit Checklist
Active Pharmaceutical Ingredients

	Yes	No	Comment
e. Does the quality unit review and approve procedures affecting the quality of intermediates or APIs?			
f. Does the quality unit conduct internal audits?			
g. Are audits for contract manufacturers of raw materials, intermediates, and APIs conducted by the quality unit?			
1) Is a list of acceptable suppliers for each component available?			
h. Are contract laboratories audited?			
i. Who reviews and approves changes that potentially affect intermediate or API quality?			
j. Does the quality unit review and approve validation protocols and reports?			
k. Are quality-related complaints investigated and resolved by the quality unit?			
l. Who ensures that effective systems are used for maintaining and calibrating critical equipment?			
m. Who ensures that materials are appropriately tested and the results are reported?			
n. Who ensures that there are stability data to support retest or expiry dates, and storage conditions for APIs and/or intermediates, where appropriate?			
o. Does the quality unit perform product quality reviews?			
Organization and Personnel			
1. Is a current organizational chart available showing reporting structure through the President of the company?			
2. Is a written procedure for training available?			
3. Has cGMP training been completed for operators and analysts? Is it properly documented?			
4. Is job-specific training, including safety considerations, conducted for operators and analysts? Is it properly documented?			
5. Is training periodically assessed?			
6. Do employees working on this product have adequate training/ experience/qualifications for their responsibilities?			
7. Are there sufficiently trained and qualified operators and analysts to produce and test the product?			
8. If special clothing is necessary, is it described in a written policy with an established frequency of change? Are areas of use specified and/or posted?			
9. Do personnel comply with any requirement for hair coverings or special clothing, or protection in the various manufacturing, packaging, and testing areas?			
10. Is there a policy for restriction of smoking, eating, drinking, chewing, and storage of food to designated areas separate from the man-ufacturing areas?			
11. Are personnel with illness or open skin lesions that may contaminate or otherwise adversely affect the safety or quality of the product allowed to work in any operation that could cause the product to become contaminated?			
12. Do the on-site consultants have sufficient education, training, and experience to advise on the subjects for which they are retained?			

Supplier Quality Audit Checklist
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	Yes	No	Comment
a. Are their Curriculum Vitaes (CVs) and qualifications on file?			
b. Are there records of the type of service provided?			
Facilities			
1. Are the facilities of suitable size, design, and construction for manufacturing and controlling the product, and minimizing potential contamination?			
2. Are facilities completed and ready for production?			
3. Are the facilities clean and orderly, and in good repair?			
4. Are facility floor plans available?			
5. Are there defined areas or other control systems for receipt, identification, sampling, and quarantine of incoming materials, quarantine before release or rejection of intermediates and APIs, sampling of intermediates and APIs, holding rejected materials before further disposition, storage of released materials, production operations, packaging and labeling operations, and laboratory operations?			
6. Are adequate and clean washing and toilet facilities provided for personnel?			
7. Are the air handling systems appropriate and adequate for the operations being performed?			
8. Have the air handling systems been qualified and are they properly monitored?			
9. Are transfer lines, pipes, and valves labeled (contents, direction of flow, etc.) where appropriate?			
10. Are drains of adequate size, and provided with an air break or a suitable device to prevent back-siphonage, when appropriate?			
11. If purified water is part of the process, are current schematic diagrams available for the system? Has the system been validated?			
12. If the product is a controlled substance, are security provisions in compliance with the regulations in place?			
13. Is there adequate lighting? Where appropriate, in order to protect exposed product or machinery, is it equipped with protection against shattering?			
14. Is sewage, refuse, and other waste disposed of in a safe, timely, and sanitary manner?			
15. Are there are written procedures that assign responsibility for sanitation and describe cleaning schedules, methods, equipment, and materials to be used in cleaning buildings and facilities?			
16. Is there a procedure for pest control that specifies the use of approved rodenticides, insecticides, fungicides, and cleaning and sanitizing agents?			
Equipment			
1. Production and Process Controls			
a. Is equipment designed to preclude adulteration of product with lubricants, coolants, fuel, metal fragments, or other extraneous materials?			
b. Is equipment constructed so that product-contact surfaces are not reactive, additive, or absorptive, and will not adversely affect the product?			
c. Is production equipment used only within its qualified operating range?			
d. Are unique identification numbers assigned to all major equipment and instruments?			

Supplier Quality Audit Checklist
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	Yes	No	Comment
e. Are a set of current drawings maintained for equipment and critical installations?			
f. Maintenance and Cleaning			
1) Have schedules and procedures, including assignment of responsibility been established for preventive maintenance?			
2) Are there logs documenting maintenance for each piece of equipment?			
3) Is there a written cleaning procedure for each piece of equipment, including disassembly and reassembly instructions, and identifying difficult to clean parts?			
4) Is the cleaning status posted on each piece of equipment?			
5) Has each cleaning procedure been validated?			
g. Calibration			
1) Was any piece of equipment requiring calibration calibrated before use, and is it properly labeled?			
2) Does an SOP specify that equipment cannot be used if it is beyond the calibration due date? Does it describe actions to be taken if equipment is used that is found to have been beyond the due date, or is found to be out-of-calibration limits? Does it require documentation of such actions?			
3) Is calibrated equipment labeled with date of calibration and date next calibration is due?			
h. Computerized Systems			
1) Have the computerized systems been validated, or has non-validation been justified in writing?			
2) Are there established security procedures covering access and control of computers?			
3) Are there user manuals for the relevant systems?			
4) Has critical data entered manually been confirmed through an additional check?			
5) Are there established change control procedures covering computers? This includes revisions to software.			
6) Is there a secure, computer-generated audit trail that records the date and time of operator entries, and actions that create, modify, and delete electronic records?			
7) Are there incidents related to computerized systems that could affect the quality of intermediates or APIs? Has the reliability of records or test results been recorded or investigated?			
8) Have appropriate back-ups been maintained and retrievability of records been verified?			
Documentation And Records			
1. Documentation			
a. Is there an SOP for writing, handling, and updating SOPs? Are SOPs periodically reviewed and updated?			
b. Is a history of SOP revisions maintained?			
c. Is there a procedure for retention of documents (e.g., development history reports, scale-up reports, technical transfer reports, process			

Supplier Quality Audit Checklist *Active Pharmaceutical Ingredients*	Yes	No	Comment
validation reports, training records, production records, control records, and distribution records)?			
d. Are production, control, and distribution records maintained for at least one year from the expiry date of the batch?			
e. Are records for APIs with retest dates retained for at least three years after the batch has been distributed?			
f. Are specifications established and documented for raw materials, intermediates where necessary, APIs, and labeling and packaging materials?			
g. Are acceptance criteria established and documented for in-process controls?			
2. Equipment Cleaning			
a. Do records of equipment use, cleaning, sanitation, and/or sterilization and maintenance show the date, time (if appropriate), product, and batch number of each batch processed in the equipment, and the person who performed these activities?			
3. Records of Raw Materials, Intermediates, API Labeling, and Packaging Materials			
a. Are records maintained that include the name of the manufacturer, identity, quantity of each shipment of each batch of raw materials, intermediates, or labeling and packaging material, supplier's control number, number allocated on receipt, and date of receipt for APIs?			
b. Are the results from testing and examination of raw materials, intermediates, and labeling or packaging materials maintained?			
c. Are records tracing the use of materials available?			
d. Is documentation available showing the examination and review of API labeling and packaging materials?			
e. Are records of the disposition of rejected raw materials, intermediates, or API labeling and packaging materials available?			
4. Master Production and Control Records			
a. Do master production and control records include the following:			
1) The name of the intermediate/API being manufactured, and an identifying document reference code, if applicable?			
2) A list of all raw materials and intermediates?			
3) The quantity or ratio of each raw material or intermediate, including the unit of measure?			
4) The production location and major production equipment to be used?			
5) Detailed production instructions including sequences to be followed, ranges of process parameters to be used, sampling instructions, in-process controls, time limits, and expected yield ranges?			
5. Batch Production and Control Records			
a. Are batch records identified with a unique batch or identification number, dated, and signed when issued?			
b. Do batch production records include:			
1) Dates, and when appropriate, times?			
2) Identity of major equipment?			
3) Specific identification of each batch, including weights, measures, batch numbers of raw materials, intermediates, or any			

Supplier Quality Audit Checklist *Active Pharmaceutical Ingredients*	Yes	No	Comment
reprocessed materials used during manufacturing?			
4) Actual results recorded for critical process parameters?			
5) Any sampling performed?			
6) Signatures of the persons performing, supervising, or checking each critical step?			
7) In-process and laboratory test results?			
8) Actual yield at appropriate phases or times?			
9) Description of packaging and label for intermediate or API?			
10) Representative label of API or intermediate?			
11) Deviations that may have occurred and investigations conducted?			
12) Results of release testing?			
6. Laboratory Control Records			
a. Are all data retained for tests to ensure compliance with established specifications and standards?			
b. Are records of all calculations performed in connection with the test available?			
c. Is the signature of the person performing the test and the date of the test present on the record?			
d. Have the records been reviewed for accuracy, completeness, and compliance with established standards by a second person?			
e. Have records of modifications been established? Have analytical methods been maintained?			
f. Are there calibration records for lab instruments, apparatus, gauges, and recording devices?			
g. Do records exist for all stability testing performed on APIs?			
h. Are records of OOS investigations maintained?			
7. Batch Production Record Review			
a. Are written procedures available for the review and approval of batch production and lab control records, including packaging and labeling?			
b. Are all deviation, investigation, and OOS reports reviewed before the batch is released?			
c. Has the quality unit reviewed all production and lab control records prior to release of the API?			
Materials Management			
1. General Controls			
a. Are there written procedures for the receipt, identification, quarantine, storage, handling, sampling, testing, and approval or rejection of materials?			
b. Is there a system for evaluating suppliers of critical materials?			
c. Are materials purchased against an agreed specification approved by the quality unit?			
d. Does the site's change control program apply to changing the source of critical raw materials.			
2. Receipt And Quarantine			
a. Are containers of incoming raw materials inspected upon receipt for labeling of contents, container damage, broken seals, and ensuring that their condition has not contaminated the material or caused			

Supplier Quality Audit Checklist
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	Yes	No	Comment
deterioration? Are these inspections documented?			
b. Are written procedures for pumping bulk tank materials available?			
c. Are bulk tank materials sampled and released prior to transfer?			
d. Are bulk deliveries made from non-dedicated tankers? If so, is there assurance that no cross-contamination occurred?			
e. Does each container or grouping of containers have its own code, receipt, or batch number?			
3. Sampling and Testing Of Incoming Production Materials			
a. Is identity testing performed on each batch of raw material received?			
b. If a reduced testing program is used, does it ensure that a complete analysis is performed at appropriate intervals?			
c. Do sampling methods specify the number of containers to be sampled?			
d. Is sampling conducted at defined locations, and by procedures designed to prevent contamination of the material being sampled?			
e. Do containers that have been sampled marked to indicate that sampling has occurred?			
4. Storage			
a. Are materials handled and stored in a manner to prevent degradation, contamination, and cross-contamination?			
b. Are materials stored under conditions, and for a time period, that have no adverse effects on their quality? Are they controlled such that FIFO is used?			
c. Are rejected materials identified and controlled under a quarantine system?			
5. Reevaluation			
a. Are materials reevaluated to determine their suitability for use?			
Production and In-Process Controls			
1. Personnel			
a. Do designated production personnel who prepare, approve, and distribute pre-approved instructions for the production of intermediates or APIs follow written procedures?			
b. Are production personnel responsible for reviewing all production batch records ensuring that they are completed and signed?			
c. Are the facilities clean and, where appropriate, disinfected?			
d. Are calibrations performed and records kept?			
e. Are the premises and equipment maintained and records kept?			
f. Are validation protocols and reports reviewed and approved?			
g. Are proposed changes in product, process, and equipment evaluated?			
h. Are new and, where appropriate, modified facilities and equipment qualified?			
2. Production Operations			
a. Are raw materials for intermediate and API manufacturing weighed or measured under conditions that do not affect their suitability for use?			
b. Are materials subdivided for later use transferred to suitable containers with identification?			
c. Are deviations documented and explained? Are critical deviations investigated and conclusions reported?			

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	Yes	No	Comment
d. Are critical weighing, measuring, or subdividing operations witnessed or subject to an equivalent control?			
e. Is the processing status of major units of equipment indicated?			
f. Are materials to be reprocessed or reworked controlled to prevent unauthorized use?			
3. Time Limits			
a. Are intermediates held for further processing stored under appropriate conditions?			
4. In-Process Sampling and Controls			
a. Are there written procedures that define in-process controls and their acceptance criteria?			
b. Are critical in-process controls stated in writing and approved by the quality unit?			
c. Are there written procedures that describe the sampling methods for in-process materials, intermediates, and APIs?			
d. Is in-process sampling performed according to a sampling plan? Are procedures designed to prevent contamination of the sampled material?			
5. Blending Batches of Intermediates or APIs			
Are the OOS batches blended with other batches for the purpose of meeting specification?			
a. Are blended batches adequately controlled, documented, and tested for conformance to established specifications?			
b. Is the batch record of the blended batch allow for traceability back to the individual batches that make up the blend?			
c. Is the expiry date of the blended batch based on the manufacturing date of the oldest tailings or batch in the blend?			
6. Contamination Control			
a. Are production operations conducted, such that contamination of intermediates or APIs by other materials, is prevented?			
Packaging and Identification Labeling of APIs and Intermediates			
1. General			
a. Are there written procedures for the receipt, identification, quarantine, sampling, examination and/or testing, release, and handling of packaging and labeling materials?			
b. Are there established specifications for packaging and labeling materials?			
c. Are records maintained for each shipment of labels and packaging materials showing receipt, examination, testing, and whether these materials were accepted or rejected?			
2. Packaging Materials			
a. Do containers provide adequate protection against deterioration or contamination of the intermediate or API?			
b. Are containers clean and are not reactive, additive, or absorptive so as to alter the quality of the intermediate or API?			
c. Are reused containers cleaned? Have all previous labels have been removed or defaced?			
3. Label Issuance and Control			

Supplier Quality Audit Checklist *Active Pharmaceutical Ingredients*			
	Yes	**No**	**Comment**
a. Are labels stored in a secured area with access limited to authorized personnel?			
b. Is there an SOP for receiving, handling, storing, and reconciliation of labels?			
c. Are investigations conducted if discrepancies are found between the number of containers labeled and the number of labels issued? Does the quality unit approve these investigations?			
d. Are excess labels bearing batch numbers, obsolete and out-dated labels destroyed?			
e. Are printed labels carefully examined for proper identity and conformity to specifications in the master production record?			
f. Are printing devices used to print labels for packaging operations controlled to ensure that all imprinting conforms to the print specified in the batch production record?			
g. Is a printed label representative of those used included in the batch production record?			
4. Packaging and Labeling Operations			
a. Are there complete written instructions for packaging and labeling?			
b. Are labeling operations adequately separated to preclude cross-contamination and mix-ups?			
c. Are labels used on containers of intermediates or APIs indicate the name or identifying code, batch number, and storage conditions when such information is critical to ensure the quality of the intermediate or API?			
d. Does the inspection of the packaging and labeling facilities performed immediately before use ensure that all materials not needed for the next packaging operation have been removed? Is this documented in the batch production records?			
e. Are packaged and labeled intermediates or APIs examined during the packaging operation to ensure that containers and packages in the batch have the correct label? Is this examination recorded in the batch production record?			
f. Are intermediates or APIs transported outside of the manufacturer's control labeled with the manufacturer's name and address, quantity of contents, special transport conditions, expiry date as needed, and retest date if applicable?			
g. If intermediates or APIs are transported outside of the manufacturer's control, are the containers sealed, such that if the seal is breached or missing, the recipient will be alerted to the possibility that the contents have been altered.			
Storage And Distribution			
1. Warehousing Procedures			
a. Are temperature and humidity controlled appropriately for materials stored in the warehouse to protect against deterioration and physical, chemical, or microbial contamination? Is the temperature and humidity monitored?			
b. Is there a system to prevent the unintentional or unauthorized use of quarantined, rejected, returned, or recalled materials?			

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	Yes	No	Comment
2. Distribution Procedures			
a. Does the quality unit release APIs and intermediates to distribution to third parties?			
b. Are APIs and intermediates transported in such a manner that does not affect their quality?			
c. Is there a system in place to ensure that the transporter has been made aware of proper shipping and storage conditions, and is complying with them?			
d. Is there a system in place by which the distribution of each batch of intermediate and/or API can be readily determined to permit its recall?			
Laboratory Controls			
1. General Controls			
a. Are there procedures describing sampling, testing, approval, or rejection of materials, and recording and storage of laboratory data?			
b. Are specifications, sampling plans, and test procedures, as well as changes to them, written by the appropriate organizational unit and approved by the quality unit?			
c. Are action limits set where applicable, e.g., for total microbial count, objectionable organisms, endotoxins, etc.?			
d. Is there an SOP for investigation of OOS analytical results and retesting that includes a time limit for completing investigations? Is it being followed? Are investigations completed and matters resolved in a reasonable period of time? Do conclusions and corrective actions appear to be adequate?			
e. Are reagents and standard solutions prepared and labeled according to written procedures? Are "Use By" dates applied, as appropriate?			
f. Are primary reference standards stored and maintained in accordance with manufacturer's instructions?			
g. Are in-house primary standards used? Has testing been performed to fully establish the identity and purity of the in-house primary standard?			
h. Are secondary standards used? Are they periodically requalified in accordance with a written protocol?			
2. Testing of Intermediates and APIs			
a. Has an impurity profile been established that includes the identity or some qualitative measure (e.g., retention time) of the impurity, range of the impurity observed, and classification of each identified impurity?			
b. Is the impurity profile periodically compared to the impurity profile in the regulatory submission or compared against historical data?			
3. Certificate of Analysis (CA)			
a. Does the certificate of analysis include the name of the intermediate or API (and its grade, where appropriate), batch number, date of release, and each test performed including test results and acceptance limits?			
b. Are the certificates signed and dated by authorized personnel in the quality unit? Do they include the name, address, and telephone number of the manufacturer?			

Quality Audit Checklist
Active Pharmaceutical Ingredients

	Yes	No	Comment
c. If repackers/reprocessors, agents, or brokers are used, do the certificates show the name, address, and telephone number of the laboratory that performed the analysis?			
4. Stability Monitoring of APIs			
a. Are test procedures used in stability testing validated and stability-indicating?			
b. Are stability samples stored in containers that simulate the market container?			
c. Is one batch per year of API manufactured included in the stability program and tested annually?			
d. If stability testing is performed, is it conducted according to intervals and tests specified in a stability protocol? Is it within the specified cycle times appropriate for the test intervals?			
e. Are stability failures investigated and reported to management?			
f. Are storage conditions consistent with ICH guidelines?			
5. Expiry And Retest Dating			
a. Are expiry and retest dates based on an evaluation of data derived from stability studies?			
b. Are representative samples used for the purpose of performing a retest?			
6. Reserve Samples			
a. Are reserve samples retained for one year after the expiry date of the batch, or three years after distribution of the batch, whichever is longer?			
b. Is the reserve sample stored in the same packaging system in which the API is stored, or one that is equivalent to, or more protective than the marketed packaging system?			
Validation			
1. Validation Policy			
a. Is the company's policy, intentions, and approach to validation documented?			
b. Are critical (API) product attributes, i.e., process parameters, affecting critical quality attributes? Are ranges for critical process parameters defined?			
2. Validation Documentation			
a. Are written validation protocols used that specify how validation will be accomplished? What are the critical process steps and acceptance criteria? Does the quality unit approve the protocols?			
b. Do validation reports include results obtained? Do these reports discuss any deviations observed and recommend changes to correct deficiencies?			
3. Qualification			
a. Have design, installation, operational, and performance qualifications been performed for critical equipment and ancillary systems? Have these activities been documented?			
4 Process Validation			
a. Has the current process been validated (i.e., defined in terms of raw materials, processing steps, operating parameters, process limitations, and key tests needed for process control, and demonstrated to operate consistently to assure that API meets established specifications)?			

Supplier Quality Audit Checklist
Active Pharmaceutical Ingredients

	Yes	No	Comment
b. Are periodic reviews of systems and processes conducted to verify that they are still operating in a validated state?			
5. Cleaning Validation			
a. Does validation of cleaning procedures reflect actual equipment usage patterns?			
b. Is the selection of an intermediate or API for cleaning validation based on the solubility or difficulty of cleaning?			
c. Is the calculation of residue limits based on potency, toxicity, and stability?			
d. Have analytical methods been validated to demonstrate they have the required sensitivity to evaluate cleaning validation samples?			
e. Does sampling include swabbing, rinsing, or alternative methods (e.g., direct extraction), as appropriate, to detect insoluble and soluble residues?			
f. Are cleaning procedures monitored at appropriate intervals after validation to ensure that these procedures are effective when used during routine production?			
6. Validation of Analytical Methods			
a. Are records of modifications to validated analytical methods maintained?			
b. Has equipment used to carry out method validation been calibrated and qualified for use?			
Change Control			
1. Does an adequate system exist, described in an SOP, for controlling changes within the production process? Does it include review and approval of changes to processes, test methods, specifications, documents, and equipment? Does it require evaluation of the need for re-qualification or revalidation?			
2. Is the quality unit involved in the change control process?			
3. Is the potential impact of the proposed change based on the quality of the intermediate or API evaluated?			
4. After a change has been implemented, is there an evaluation of the first batches produced or tested?			
5. Is there a system in place to assure that significant process changes and their effect on the product are communicated to the client?			
Rejection and Requalification of Material			
1. Is the final disposition of rejected material always recorded?			
2. Are controls in place to prevent formation of by-products and over-reacted materials in reprocessing operations?			
3. Is an investigation performed into the reason for nonconformance prior to reworking batches?			
4. Are reworked batches, subject to testing and evaluation requirements, demonstrate that the reworked product is of equivalent quality to that produced by the original process?			
5. Are there approved procedures for the recovery of reactants, intermediates, or the API? Do the recovered materials meet specifications suitable for their intended use?			

Supplier Quality Audit Checklist
Active Pharmaceutical Ingredients

	Yes	No	Comment
6. Are returned intermediates or APIs identified as such and quarantined?			
7. Are records of returns maintained? Is the use or disposal of the returned material documented?			
Complaints and Recalls			
1. Is there an adequate program, described in an SOP, for handling complaints, maintaining complaint records, conducting complaint investigations, and implementing corrective actions where indicated? Is there a target timeframe for responding?			
2. Is the effectiveness of corrective actions verified?			
3. Are trend analyses performed?			
4. Is there a written recall procedure that defines the circumstances under which a recall of an intermediate or API should be conducted?			
5. Does the recall procedure specify who evaluates the information, how the recall should be initiated, who should be informed, and how the recalled material should be treated? Does it define reporting requirements for serious or potentially life-threatening situations?			
Contract Manufacturers and Laboratories			
1. Are contractors (including laboratories) evaluated to ensure GMP compliance? Are audits of contractors conducted?			
2. Is there a written agreement or contract between the company and its contractors that defines GMP responsibilities, including the quality measures, of each party?			
3. Are manufacturing and laboratory records maintained at the site where the activity occurs? Are the records readily available?			
4. Are changes in the process, equipment, test methods, specifications, or other contractual requirements approved by the contract giver prior to implementation?			
Agents, Brokers, Traders, Distributors, Repackers, and Relabellers			
1. Are documents retained by agents, brokers, etc. include the name and address of the original manufacturer, purchase order information, bills of lading, receipt information, name or designation of API or intermediate, manufacturer's batch number, transportation or distribution records, certificates of analysis, and retest or expiry dates?			
2. Does the agent, broker, etc. have an adequate system for quality management?			
3. Is repackaging, relabeling, and holding of APIs or intermediates subject to GMP controls?			
4. Have stability studies been conducted to justify assigned expiration or retest dates if the API or intermediate is repackaged in a different type of container?			
5. Do agents, brokers, etc. transfer all quality or regulatory information received from an API or intermediate manufacturer to the customer, and from the customer to the API or intermediate manufacturer?			
6. Are records of complaints and recalls maintained? Are responses from the original API or intermediate manufacturer maintained on file?			
7. Are records of returns maintained on file?			

Section Seven:

Supplier Quality Audit Report

Audit Reference Number:	_____
Audit Category:	Inactive Component ❑ Active Component ❑ Packaging Component ❑
Company Name and Address:	_____
Assessment Period:	_____
Lead Auditor:	_____
Audit Team Members:	_____
Audit Purpose:	_____
Audit Scope:	_____
Rationale:	_____
Performance Standards Used:	GMP ❑ ISO ❑ Other:
Prior Assessment History:	_____
Attachments:	_____
Personnel Interviewed:	_____
Background/History of Company:	_____
Procedures Reviewed:	_____
Equipment List:	_____

Executive Summary

Audit Report Narrative

_____

Audit Observations/Comments:

Audit Report Prepared By:	_____
Title and Department:	_____
Date Issued:	_____

Audit Rating:

Acceptable ❑ Provisional ❑ Unacceptable ❑

Section Eight:

Frequently Asked Questions (FAQs) on Supplier Qualification Programs

Q: *Do pharmaceutical regulations require that components meet specification and quality requirements?*

Yes. All international GMP regulations require that starting materials, including packaging materials, meet required specifications and quality requirements prior to use. For example, these requirements are exemplified in the World Health Organization (WHO) GMPs under Section 13., European GMPs under Section 4.0, Canadian GMPs under Section C.02.009, and U.S. GMPs under 21 CFR 211.84.

Q: *Do ISO regulations apply to supplier qualification?*

The ISO 9001 and ISO 9002 quality standards require manufacturers to select vendors on the basis of their ability to meet purchase specifications, which by ISO 9004 definition include regulatory requirements/safety standards, and to maintain records of acceptable vendors.

Q: *Can my company accept components and packaging materials from a supplier by simply receiving the supplier's certificate of analysis?*

No. GMPs require that the manufacturer determine the reliability of the test results that are reported by the supplier for the purchased material. For example, under FDA's cGMP regulations, 21 CFR 211.84(a) through 21 CFR 211.84(e) requires a manufacturer to test and approve or reject components, drug product containers, and closures. 21 CFR 211.84(d)(2) specifically requires that manufacturer to test each component for conformity with written specifications for purity, strength, and quality, or accept the supplier's report of analysis. 21 CFR 211.84(d)(3) requires the manufacturer to test containers and closures for conformance with all appropriate written procedures or accept the supplier's report of analysis. However, restrictions apply to accepting reports of analysis in maintaining compliance with either of these CFR sections. The restrictive conditions specified in the cGMP regulations for acceptance of a vendor's report of analysis for components are the manufacturer must conduct at least one specific identity test on each lot received, and the reliability of the supplier's analysis must be established through validation of the supplier's test results at appropriate levels.

Q: *Can my company accept components and packaging materials on a supplier's certificate of analysis, since we only manufacture clinical trial material?*

No. The FDA cGMPs apply to all drugs that are intended for human use. The cGMP regulations, Title 21 of the Code of Federal Regulations (CFR), Parts 210 and 211, are binding regulations. This means they have the force and effect of law. The regulations interpret the statutory requirement for production of drugs in compliance with cGMPs, found in section 501(a)(2)(B) of the Federal, Food, Drug and Cosmetic Act (FD&C Act). The Act itself makes no distinction between finished pharmaceuticals, APIs, clinical supplies, and commercial products. In addition, the FDA's position on the applicability of the GMP regulations is articulated in Comment 49 in the Preamble section to the current GMP regulations published 29 September 1978. It states "the Commissioner finds that as stated in section 211.1, these GMP regulations apply to the preparation of any drug for administration to humans, including those still in the investigational stages."

The FDA cGMPs apply to all drugs that are intended for human use. The cGMP regulations, Title 21 of the Code of Federal Regulations (CFR), Parts 210 and 211, are binding regulations.

Q: *How many lots of material must be tested before my company can enter into a reduced testing program with a supplier?*

While there is no specific number stated in the FDA cGMPs, a minimal number of consecutive lots of a material required before a reduced testing can be employed. It can usually be defined as three, the statistically minimal number to demonstrate confidence.

Q: *What are some of the requirements for setting up a supplier qualification program?*

There are several acceptable approaches to a supplier qualification program. A document outlining the specific responsibilities of each party is required. At a minimum, the procedure should specify the content and format of the certificate of analysis, and outline the change control notification process from the supplier to the manufacturer. In addition, historical data should be available from the supplier that verifies that the process for the raw material is under a state of control. In addition, an on-site audit of the supplier's facilities, and controls by the manufacturer's QA department should also be conducted.

Q: *What are the qualification levels that a supplier is assigned by the manufacturer?*

Typically, a rating system is set up using several distinct levels of qualification. For example, approved, preferred, and certified may be used. Approved could be defined as a supplier that has passed an initial GMP audit by the manufacturer, and where full release testing by the manufacturer is required. The preferred status could be defined as a supplier who has maintained the quality audit status by the manufacturer, and where a database has been acquired of verification testing by the supplier. The certified status should be reserved for those suppliers that have exhibited a good quality audit rating through time during the approved and preferred status levels, and also where full release testing has demonstrated reliability of the supplier's test results by the manufacturer. After reaching the certified status, the designated material(s) received by the supplier can be accepted on the supplier's certificate of analysis and minimal (identity test) by the manufacturer.

Q: *How long is the qualification rating of a supplier good for?*

The supplier qualification program should include a procedure that requires periodic full release testing, such as every tenth lot of the material purchased. In addition, the procedure should describe how failure test results, upon retesting by the manufacturer and subsequent requalification of the supplier, are to be addressed. Also list the types of lots (e.g., reprocessed lots) that are not subject to the reduced testing program. The supplier qualification program should require an entire reassessment of the supplier, no matter what the supplier qualification level is, i.e., approved, preferred or certified, when testing by the manufacturer shows failing test results, or the supplier is found to have serious GMP deficiencies during a surveillance audit by the manufacturer.

Q: *How should the status for each supplier entered in the supplier qualification program be documented?*

Normally, a document should be issued by the QC or QA/Compliance department for each supplier verifying that the criteria for qualification has been satisfied.

Q: *Should a supplier be given an approved status by material, site, or company name?*

It depends. Each material (i.e., type, grade) procured by the manufacturer from the supplier should be evaluated separately. This includes verification testing, as well as supplier quality audits. When conducting the supplier quality audit, the quality system and manufacturing procedures for the material(s) that are currently being purchased are evaluated. Under some circumstances, another material the manufacturer wishes to purchase from the supplier may be manufactured under non-GMP conditions. Based on this, suppliers should be qualified by the material(s) that the manufacturer is currently deciding to purchase. ❑

About the Author

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Article Acronym Listing

API:	Active Pharmaceutical Ingredient
CA:	Certificate of Analysis
CAPA:	Corrective And Preventive Action
CFRs:	Code of Federal Regulations
cGMP:	current Good Manufacturing Practice
CV:	Curriculum Vitae
DHHS:	Department of Health and Human Services
DMF:	Drug Master File
EIR:	Establishment Inspection Report
EMEA:	European Agency for the Evaluation of Medicinal Products
ERP:	Enterprise Resource Planning
FAQ:	Frequently Asked Question
FDA:	Food and Drug Administration
FD&C Act:	Federal, Food, Drug and Cosmetic Act
FIFO:	First In First Out
HPFB:	Health Products and Food Branch
ISO:	International Organization for Standardization
JIT:	Just-In-Time
NDA:	New Drug Application
OOS:	Out-of-Specification
OTC:	Over-the-Counter
PLC:	Programmable Logic Controller
QA:	Quality Assurance
QC:	Quality Control
SCADA:	Supervisory Control and Data Acquisition
SF:	Supplier File
SPC:	Statistical Process Control
WHO:	World Health Organization

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Auditing The Training Function

Periodic audits are used to verify the existence of, and the effectiveness of systems, procedures, and other controls to ensure that manufacturing and testing are consistently accomplished within specified parameters.

by
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Training is a Current Good Manufacturing Practice (cGMP) requirement. Like other cGMP requirements, this function should be periodically audited to verify that it is working as intended. A summary of key points to be evaluated in an audit is provided in this article. These points may be used to construct a customized checklist for training audits.

The regulatory requirement to have adequately trained personnel to perform the various tasks associated with the manufacture of drug or medical device products is as much a part of the regulation as manufacturing and laboratory controls. Periodic audits are used to verify the existence of, and the effectiveness of systems, procedures, and other controls to ensure that manufacturing and testing are consistently accomplished within specified parameters. The audit of the training function has the same objective. Since training is the method that most personnel learn how to perform their tasks, adding the training function to audits will provide additional and useful insight into the capability of personnel who are assigned the various cGMP-regulated tasks. While this article is primarily written for internal audits, many of the points mentioned may be equally useful in conducting vendor or contract service provider audits. Although the tasks of manufacturing medical device products may differ considerably from those employed to make pharmaceutical products, the overall approach to auditing the training process applies to either.

If the reader desires more background on Food and Drug Administration (FDA) concerns about training, examples are provided in *Figure 1*.

The Regulatory Requirement

Just like other requirements, the need for training is detailed in both the cGMP regulations for drug and medical devices. They are provided here for the reader's convenience.

§ 211.25 Personnel qualifications

(a) Each person engaged in the manufacture, processing, packing, or holding of a drug product shall have education, training, and experience, or any combination thereof, to enable that person to perform the assigned functions. Training shall be in the particular operations that the employee performs and in current good manufacturing practice (including the current good manufactur-

ing practice regulations in this chapter and written procedures required by these regulations) as they relate to the employee's functions. Training in current good manufacturing practice shall be conducted by qualified individuals on a continuing basis and with sufficient frequency to assure that employees remain familiar with cGMP requirements applicable to them.

(b) Each person responsible for supervising the manufacture, processing, packing, or holding of a drug product shall have the education, training, and experience, or any combination thereof, to perform assigned functions in such a manner as to provide assurance that the drug product has the safety, identity, strength, quality, and purity that it purports or is represented to possess.

(c) There shall be an adequate number of qualified personnel to perform and supervise the manufacture, processing, packing, or holding of each drug product.[1]

§ 820.25 Personnel

(a) General. Each manufacturer shall have sufficient personnel with the necessary education, background, training, and experience to assure that all activities required by this part are correctly performed.

(b) Training. Each manufacturer shall establish procedures for identifying training needs and ensure that all personnel are trained to adequately perform their assigned responsibilities. Training shall be documented.

(1) As part of their training, personnel shall be made aware of device defects which may occur from the improper performance of their specific jobs.

(2) Personnel who perform verification and validation activities shall be made aware of defects and errors that may be encountered as part of their job functions.[2]

Notice that the regulation alludes to the competence of personnel, which implies that the training has been effective. The regulation doesn't merely say, "provide training sessions." If the training is ineffective or inadequate, personnel competence to perform a specified task is not a certainty. The writer feels that the intent of the regulatory requirements are to enable personnel to perform tasks correctly. If the training provided falls short of that, the training has not met the intent of the regulation. This is one of the key questions to be answered in the audit.

One is typically obliged to ask a variety of questions in determining the effectiveness of the training function. Those questions may center on many or all of the following training issues:

- Is the training function clearly assigned?
- Is the assignment of responsibility in writing?
- Is there an overall training program with discreet modules for orientation, SOP training, periodic retraining?
- Does training include the "why" or the "rationale" for specified steps?
- Are the trainer or trainers qualified?
- How are they qualified?
- Is training conducted with sufficient frequency?
- How is this frequency established? What about the need to retrain?
- Is training or learning evaluated to ensure competency?

This is accomplished through tests, observation, and other methods including:

- Is evaluation against written standardized criteria?
- Is on-the-job training evaluated. How is it accomplished?
- Are written training records kept in a central location (often part of human resources)?
- Are written training records kept on a departmental basis?
- Are training records complete, accurate, and current?
- Can you verify that training records match job training requirements for at least three employees in each department?
- Do training records indicate gaps in training (whether through a manual comparison of paper records or through a query to an electronic database), i.e., who hasn't been trained?
- Are employee errors recorded, and used to determine if retraining may be required?
- Are training gaps addressed promptly through make-up training sessions?
- Is the training function audited with sufficient frequency?
- How is the frequency determined?
- Have previously identified deficiencies been corrected in a timely fashion?

In addition to the issues listed, other sources may also be useful. Reviewing the Annual Product Reviews (APRs) prepared by the company for two or three consecutive years will provide useful insight into the volume and diversity of the operation and, importantly, clues into a company's state of control if failed or reworked batches of product are more than a few. Bear in mind that failures may be higher if a new product has been added to a particular site, although, realistically, one would hope that appropriate technology transfer would prevent a high failure rate. What about complaints and the trending of complaints? Any clues on training here?

Does the organization have a stated training policy or a training Standard Operating Procedure (SOP)? If either of these exist, they will provide a starting point to compare what the audit finds against what the procedure or policy expects.

Neither the cGMP regulation for medical device or drug product manufacture requires a firm to have a training department, therefore the audit should determine that the function is assigned, performed, and documented. Regardless of how the training function is organized or to whom assigned, is the person(s) who provide the training qualified? The regulation does not offer the specifics of what constitutes qualification, so the writer offers a practical approach to qualification through several questions:

- Does the trainer have the technical expertise required to train on the assigned subject?
- Does the trainer have knowledge of company specific SOPs to train on the assigned subject?
- Does the trainer have training expertise?

These are not absolute requirements, but they broadly represent the ideal. If any of these are absent, the effectiveness of the training may be less than optimal.

Frequency of training and retraining is determined by subject companies. Retraining may not be routinely required for a process or operation that is repeated with high frequency, such as once or twice a week for much of a year. But the converse creates a true training challenge. What if a particular product is manufactured only once per year, or less, and further, there are difficult and unusual steps involved? Although a person may have been trained on the procedures 18 months ago, is that person ready to make a batch today if that knowledge has never been used before? Again, the key question is: "Is the person competent to manufacture the subject product today?"

What about changes in SOPs? When are employees retrained and by whom and how? What records are available to support the training? There's a significant difference between training and understanding, versus a sheet of paper that merely suggests that training occurred.

If you may, chat with several employees about critical SOPs on which they have been trained according to records. Can you verify through a series of questions that these employees understand the SOPs well enough to perform the tasks? It's best to assure these employees that you're merely verifying their understanding of operating procedures and you're not there on a 'witch hunt.'

A sign-in sheet for a particular training session is a typical and useful start for documentation. Verify that such records are available, including: title of the training session, number or abbreviation for the session if one is assigned, date of the training session, length of the training session in hours, and instructor or instructors name(s).

If individual entries are then transcribed from these sign-in sheets into an employee's personal training record, how is the accuracy of the transcription verified? Regardless of how training records are maintained – paper system or electronic database – can one verify who has been trained and who has not been trained on specific modules? Review a sufficient number of training records to ensure that records are consistent, current, and accurate. Looking at the records for at least three employees in at least three different departments would be a reasonable start.

If an electronic database is used, then conformance with the applicable sections of 21 CFR11, the regulation for Electronic Records and Electronic Signatures, will apply. Such a review and determination are beyond the scope of this article.

Regardless of the method used to store training records, review enough of them to ensure that records are consistent, current, and accurate.

Once you have verified that training occurred, take a look at the materials used for the training. What did the learner see, listen to, or work with? Is a handout available for your inspection? What about videos, audio tapes, PowerPoint® presentations? Was a confirmation quiz used? Did all employees pass the quiz? All of these elements relate to the consistency of the training provided.

Figure 1

Examples of Training Deficiencies From FDA Warning Letters

While the writer cannot speak for the FDA, the writer has heard a consistent and recurring message at various FDA industry training workshops and seminars in recent years. Simply stated, FDA's firm inspection programs identify deficient or inadequate training in a variety firms on an on-going basis. A review of Warning Letters posted on the FDA web site at http://www.fda.gov/foi/warning.htm offers examples to support the statement just made. Training is not mentioned in every Warning Letter because sometimes FDA field personnel merely identify the impact of the inadequate training, such as "failure to follow procedures," "failure to keep adequate records," or "failure to record and justify deviations," rather than speculate on why deficiencies have been observed. If a pattern of mistakes are observed, it is then not uncommon to review the training program and training records.

"4. Failure to establish written procedures for the training of individuals involved in the gaseous and liquid medical oxygen operations [21 CFR 211.25(a)] . Investigator [redacted] observed that your firm has no written procedure for training. Your firm is expected to establish detailed written procedures (training program) outlining the specific areas of the firm's operation to be covered. On-the-job training is acceptable, as long as the training is conducted by a qualified individual." [d1466b][3]

"Failure to have in place an adequate organizational structure and sufficient personnel to assure devices are manufactured in accordance with the QS regulation and to establish a formal Quality Assurance program including the establishment of written procedures that address management responsibility, quality audits, personnel, training, design controls, corrective and preventive action, and nonconforming product review." [d1452b]

"Following recognition of the initializing variables problem trend, no formal documented training was provided to key personnel to prevent its recurrence, e.g. training of programmers, software engineers, and quality assurance personnel." [d1718b][3]

"Failure to establish procedures for identifying training needs and ensure that all personnel are trained to adequately perform their assigned functions. [21 CFR 820.25(b)l For example, there are no written procedures or documentation describing any training activities provided to your employees regarding their assigned functions or the requirements of your quality system procedures." [m598n][3]

"Failure to establish and maintain procedures for identifying training needs to ensure that all personnel are adequately trained to perform their assigned responsibilities and for maintaining required training records." [d1360b][3]

"211.25 Personnel qualifications. The training program fails to assure your employees and supervisory employees are trained in the specific tasks and in their assigned responsible functions. Examples from FDA-483 Item number 5 are:

a. There are no written procedures for conducting training for specific tasks or for good laboratory practice training. 211.25(a)
b. The training records do not sufficiently document that analysts have been trained for the specific tasks that they perform. 211.25(a)
c. There is no documentation that management reviewed the adequacy of the training. 211.25(b)." [m5089n][3]

"You failed to specify how initial training of new employees would be conducted, as required by 21 CFR 820.25, in your procedure QO03, "Personnel." [g1728d][3]

"Failure to document training to ensure that all personnel are trained to adequately perform their assigned responsibilities [21 CFR 820.25(b)]. For example:

a. Training files for laboratory technicians [redacted] contain no documentation that they were trained in [redacted]
b. There is no documentation to show that technician 'was retrained after making multiple errors in QC testing.
c. Required supervisor signatures were missing in the training records of the current, recently promoted, QC supervisor." [m3150n][3]

"Failure to provide training that is adequate to enable employees to perform their assigned duties and func-

Figure 1

Examples of Training Deficiencies From FDA Warning Letters *(Continued)*

tions as required by 21 CFR211 .25 (a). For example, there is no written evidence that employees have received proper training in the [redacted] and current Good Manufacturing Practice. [m3681n][3]

"Failure to have personnel responsible for supervising the manufacture, processing, packing or holding of drug products with sufficient education, training, and experience to perform their assigned functions so as to assure that drug products have the safety, identity, strength, quality, and purity they purport [21 CFR 21 1.25(b)]. Specifically, the Operations Manager, who has been in this position at the facility on [redacted] for seven months, has not received cGMP training for drug products. This manager also has distribution authority over drug products at your facilities in [four sites named]. [g1150d][3]

The reader may download the complete Warning Letters by entering the following complete address: www.fda.gov/foi/warning.htm

These letters are stored in Portable Document Format (*.pdf) and must be read by the Adobe Reader program, which is available for free download from the FDA web site as well as **IVT**'s web site and others.

For on-the-job training, is a standard checklist used to verify the employee can demonstrate the required knowledge and skill? Who administers the review? Are these reviews available for review?

Conclusion

Training is a regulatory requirement. Because it's a part of the regulation, and has direct bearing on the knowledge and skills of operating and testing personnel, the function should be periodically audited. Auditing the training function of a firm need not be an overly complicated task. By knowing what to look for – based on preparation and augmented by clues from other aspects of operations – an effective approach to conducting such an audit will be made easier. ❑

About the Author

David E. Jones, M.S., R.Ph., is the founder of Biz-Tech Associates, a training and consulting service, which trains and audits client companies on drug and medical device cGMPs. He was formerly a Vice President of A. H. Robins Company where he was responsible for four business units that manufactured Active Pharmaceutical Ingredients (APIs) and pharmaceutical products. Previously, he provided training and consulting on a contract basis to clients of GMP Institute and ISPE, and has worked with the FDA on several training-related projects. He can be reached by phone at 804-639-6655, or by e-mail at cGMPman@aol.com.

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1. The Current Good Manufacturing Practice Regulation for Finished Pharmaceuticals, 21 CFR 211, 43 FR 45076, September 29, 1978 as amended through October 2001 when downloaded.
2. The Current Good Manufacturing Practice Regulation for Medical Devices, 21 CFR 820, 1996.
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Suggested Reading

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Article Acronym Listing

API:	Active Pharmaceutical Ingredient
APR:	Annual Product Review
cGMP:	Current Good Manufacturing Practice
FDA:	Food and Drug Administration
PDF:	Portable Document Format
SOP:	Standard Operating Procedure

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GMP Auditing Techniques for Medical Device Manufacturers

A Case Study

Although the purpose and scope of some external audit teams can be somewhat difficult to follow, an effective internal audit program can be a valuable resource for those of us who look at audits as a tool that identifies areas in need of improvement.

by
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Despite the enormous effort that most of us in the medical device industry have put forth in the development of internal audit procedures, it remains a difficult task due to the fact that we must audit our systems to ensure conformance to several different standards and regulations. This article focuses on guidelines and tools that can be used for auditing quality systems of medical device manufacturers.

First of all, you'll need to determine what the level of conformance is for your quality system against Food and Drug Administration (FDA) regulatory requirements. You should review the procedures and policies your company has developed, and determine whether they meet regulatory requirements before checking to see if they are being followed.

Second, you should determine the effectiveness of the quality system that has been implemented. This requires that the company not only check whether their procedures and policies are being followed, but that they also determine whether the quality system is adequate and effective.

Third, you must ensure that the corrective actions agreed upon as a result of the previous audit have been effectively completed. Follow-up must be completed on corrective action from present and previous audits in order to ensure that any issues have been resolved.

Because most of us in the medical device industry undergo a battery of audits starting with personnel from the FDA's Office of Compliance, Office of Regulatory Affairs, the State Food and Drug Branch (FDB), a Notified ISO 9000 Body and/or Registrar, and in some cases European Regulatory Government Agencies, we sometimes tend to see audits as a nuisance rather than a tool for continuous improvement.

Although the purpose and scope of some external audit teams can be somewhat difficult to follow, an effective internal audit program can be a valuable resource for those of us who look at audits as a tool that identifies areas in need of improvement. How is this accomplished? One could start by having an effective quality systems audit program in place. The tips and methodology in this article are those that I have utilized for a number of years and found to be extremely beneficial.

Medtronic MiniMed has established and maintains procedures

for planning and implementing internal quality audits to verify the effectiveness of all quality system activities. Internal quality audits are scheduled on the basis of the status and importance of the activity to be audited, and are carried out by trained and certified personnel, independent of those having direct responsibility for the activity being audited.

The Plan and Checklist

We always start with our internal audit plan (agenda) and checklists, which are attached forms from our internal auditing procedure. We all know that we must follow our procedures for auditing in order to remain in compliance. We typically audit either by elements of the standard, or by departments, depending on how you have segmented your system for auditing. Our company uses preset checklists; our auditors will use the standard and our procedures checklist each time.

Each main activity comprising the quality system must be audited at least once a year. In addition to the annually scheduled audits, the Senior Manager of Quality Systems and Regulatory Compliance may select certain activities for more frequent auditing, depending on their status, importance, and past compliance history.

Some of the things taken into account when preparing the audit schedule are:

- Previous audit results
- Available resources
- Audit scope
- Sample size (this becomes very important when you are with a large company)
  Note: Sample size refers to the number of areas or procedures the audit schedule designates to be audited.

The key is not to try and do too much or overcommit your resources. Instead, try to schedule smaller but more frequent audits. These tend to be more effective than comprehensive three-day audits.

We contact the department to be audited at least three times prior to the scheduled audit. The first contact comes when the annual audit schedule is generated and is posted on the company intranet. The second contact is done one month prior to the audit. This allows each department time to prepare for any additional resources that may be necessary. The third contact is made about a week before the audit. We often provide those being audited with an audit schedule that allows them to prepare for the audit. In addition, one may also provide a copy of the audit checklist he/she will be using during the audit.

Audit Schedule

Our lead auditor is responsible for preparing an internal audit schedule that lists the dates audits were completed, areas to be audited, whether or not corrective action(s) was required, dates corrective actions were completed, if any, and the signature of the internal auditor. This form is presented to FDA auditors, if requested, during a GMP audit. Refer to *Figure 1.*

The schedule is developed annually (signed and dated), and updated as necessary to reflect any changes. The internal audit schedule (plan) also identifies locations (areas, departments, process, etc.) where these activities take place, and will be used to assign an audit date to each activity/location with the exception of customer-supplied product. Other areas may be added to the yearly audit plan as necessary.

Audit Plan

The lead auditor prepares and presents the audit plan to the audit team and the auditees at least one week prior to the audit. This assures that, as a minimum, the following are included:

- Audit scope
- Applicable documents
- Identification and location of activity to be audited
- Identification of organization or persons to be notified
- Scheduled date of audit
- Identification of audit checklists or procedures to be used
- Identification of audit personnel

The audit summary (*Figure 2*) is used to summarize the number of nonconforming reports and/or Corrective Action Reports (CARs) issued during the audit. This form is to be completed by the Senior Manager of Quality Systems and Regulatory Compliance and/or Lead Auditor.

Audit Checklists

The Internal Quality Audit Checklist Form (*Figure 3*) is used to evaluate and determine whether all the activities correspond with the 20 sections of ISO9001, EN46001, and Medical Device Directives (MDDs) requirements. ISO9001 is an international

Figure 1

Example Form

Internal Audit Schedule Plan

Year _____

Area/Process Audited	Schedule Date of Auditor	Date Audit was Completed	Corrective Action(s) Required? Yes/No	Signature of Auditor and Date	Corrective Action Completion Date	Corrective Action Check (√) By
Management Responsibility ISO9001, 4.1 21CFR, 820.20 (Dept. and/or area)						
Quality System ISO9001, 4.2 ISO13485, 4.2 EN46001, 4.2 21CFR, 820.5						
Contract Review ISO9001, 4.3 21CFR, 820.50						
Design Control/ Technical Files ISO9001, 4.4 ISO13485, 4.4 EN46001, 4.4 21CFR, 820.30						
Document and Data Control ISO9001, 4.5 ISO13485, 4.5 EN46001, 4.5 21CFR, 820.40						
Purchasing ISO9001, 4.6 ISO13485, 4.6 EN46001, 4.6 21CFR, 820.50						
Control of Customer Supplied Product ISO9001, 4.7	Not Applicable					

standard used to ensure that a quality system is in place and that the requirements are being followed. EN46001 and the MDD's include additional requirements to be met by medical device manufacturers. The audit checklist also helps to ensure that all Quality System Regulation (QSReg) issues comply with the specified requirements. This form is to be completed by the audit team.

Audit Personnel

Personnel assigned to carry out internal audits must be independent of those having direct responsibility for the audited activity. The Senior Manager of Quality Systems and Regulatory Compliance or a designated trained auditor may conduct audits. The trained auditor may also assist the Senior Manager of Quality Systems and Regulatory Compliance.

Figure 2

Example Form

Audit Summary Report

Internal Audit No.: _____
Date: _____

Dates: _____ to: _____ Area(s) Audited: _____
To: _____ From: _____
Vice-President Lead Auditor

Scope:

_____
_____

Audit Noncompliance (NC) or Corrective Action Request (CAR):

System Breakdown:	NC/CAR Number	Clause: (note Standard)	Description:
Yes ❑ No ❑	_____	_____	_____
Yes ❑ No ❑	_____	_____	_____
Yes ❑ No ❑	_____	_____	_____
Yes ❑ No ❑	_____	_____	_____
Yes ❑ No ❑	_____	_____	_____
Yes ❑ No ❑	_____	_____	_____

Total Number of _____ NC's and/or CAR's

Strong Points:

_____
_____

Points of Concern:

_____
_____

Assessment of Future Audit Frequency:

The consensus of the audit team is that audit frequency should (check one)

Yes ❑ Remain unchanged ❑ Be increased to: _____ per year

Auditor Qualification

All staff members performing internal audits must be trained for a minimum of 20 hours in audit principles, or possess a Certified Quality Auditor (CQA) and/or Certified Quality Engineer (CQE) certification. For more information on how to become a CQA or CQE, visit the American Society of Quality (ASQ) web site at http://www.asq.org/.

In addition, qualified external auditors may be used to conduct internal audits. The Senior Manager of Quality Systems and Regulatory Compliance will review external auditors' qualifications prior to the internal audit.

The manager and/or director responsible for the area being audited will be notified at least a week in advance of the proposed audit date. The manager will respond with a confirmation or propose an alternative date.

Closing Meeting

A post-audit meeting is conducted as part of the audit. During the closing meeting, the audit find-

Figure 3

Example Form

Internal Quality Audit Checklist

Page 1 of _____

Compliance Status

S = Satisfactory *D = Deficient* *N/A = Not Applicable*

Compliance

S	D	N/A	Audit Requirements Corresponding to ISO9001 07/94 EN46001 8/96 clauses, cGMPs, and EC-Directive 93/42/EEC Annex II, 3	Write Comments on deficiency, verification, or objective evidence, and record names, document number	Audit By: Date
			4.1 MANAGEMENT RESPONSIBILITY		
			4.1.1 QUALITY POLICY		
			A. Where are company policies and procedures documented?		
			B. Are the quality policies and procedures known and understood by staff at all levels?		
			4.1.2 RESPONSIBILITY AND AUTHORITY		
			A. Have the responsibilities of personnel whose actions affect quality been defined and documented?		
			B. Where are these responsibilities documented?		
			C. Is there an organizational chart of the company?		
			D. Where are the responsibilities for identification documented for solving quality problems?		
			E. Recording documented?		
			4.1.3 RESOURCES		
			A. Have adequate in-house resources for performing work and verification activities been identified and allocated?		
			B. Does verification include monitoring activities such as implementation of inspection and product testing?		
			4.1.4 MANAGEMENT REPRESENTATIVE		
			A. Who is given the responsibility to manage the quality program and to monitor compliance with the requirements of ISO9001, EN4001, and MDD issues?		
			B. Where is the appointment of the management representative documented?		
			C. What authority does this person have for ensuring that the quality program is implemented?		
			D. What mechanisms are in place for the reporting of the quality system performance to management?		

(Continued)

Figure 3 *(Continued)*

Example Form

Internal Quality Audit Checklist

Page 2 of _____

Compliance Status

S = Satisfactory *D = Deficient* *N/A = Not Applicable*

Compliance

S	D	N/A	Audit Requirements Corresponding to ISO9001 07/94 EN46001 8/96 clauses, cGMPs, and EC-Directive 93/42/EEC Annex II, 3	Write Comments on deficiency, verification, or objective evidence, and record names, document number	Audit By: Date
			4.1.5 MANAGEMENT REVIEW		
			A. At what intervals are management reviews held, and in what document are the frequencies stated?		
			B. Who conducts these reviews?		
			C. How are records (agendas, minutes, and reports) maintained and data utilized?		

ings are presented, and the audited organization is provided an opportunity to clarify any issues or misunderstandings. All participants are to sign the closing meeting attendance sheet.

When an item of noncompliance is noted, it is brought to the attention of, and discussed with, the responsible manager. Each noncompliance or observation is noted, and may be documented as an observation or finding on the corrective action request form.

Auditors fill out only the first part of the form, describing the noted noncompliance. The form is then handed over to the responsible manager who uses the second portion of the form to propose corrective action and a due date.

A copy of the noncompliance report is then given to the Senior Director of Quality Assurance (QA), and will be reviewed by management during the management review meeting.

Audit Reports/Corrective Action and Follow-up

The lead auditor issues an audit report within 30 calendar days after completion of the closing meeting. The report describes the findings in sufficient detail to assure corrective action can be accomplished by the audited organization.

Upon receiving the report, the responsible manager investigates the cause of the problem noted as a noncompliance, proposes a corrective action to be taken, and indicates the date by which the corrective action will be fully implemented.

The auditor, along with the Senior Manager of Quality Systems and Regulatory Compliance, reviews and approves the proposed action.

Verification And Close-Out Of Audit Findings

The lead auditor or designee ensures that follow-up is performed as necessary to close out the audit findings. On or immediately after the due date for implementation of the corrective action, the auditor follows up with an inquiry or review of corrective measures taken, or a reaudit to determine if corrective action has been implemented and determines its effectiveness.

When there is objective evidence that the corrective action is effective, the noncompliance report is closed out. When the corrective action request is closed out, a copy of the documented corrective action is given to the Senior Director of QA. Senior Management of Quality Systems and/or Regulatory Affairs will sign the verification and closeout of all audit findings.

Records

The following documents are part of the quality records, and must be retained according to established procedures:

- Auditor Qualification Records
- Audit Plans

- Completed Checklists
- Audit Reports
- Correspondence associated with corrective action, follow-up, and closeout of audits.

Internal audits, implementation of resulting corrective actions, and the follow-up audits are documented using the internal audit schedule plan form, internal quality audit checklist form, corrective action request form, and the internal audit summary form.

Part two of the corrective action request form contains a description of the nonconforming condition (to be completed by the auditor). Part four contains the proposal for a corrective action (to be completed by the responsible manager), and Part five is reserved for the follow-up audit and closeout of the report.

All records and documentation must be stamped as confidential, and the quality audit compliance team will retain the audit records.

One of the hardest things to do is get a quick turn-around time on corrective actions. Multiple priorities sometimes prevent management from responding in a timely manner. One of the ways you can help the audit team with this problem is by allowing them to offer some suggestions or possible solutions. In addition, if the auditee sees the auditors as a resource rather than as a nuisance, he/she will be much more open to the audit process, as well as suggestions to correct deficiencies found during the audit process.

One way to improve the timeliness of audit finding responses is to issue reminder notifications. Our audit finding response due dates are normally four weeks from the issue date of the finding. We typically issue "reminder of approaching due date" notifications. This documentation can be in the form of a manual memorandum/form or the more efficient e-mailed memorandum/form. Issuing reminder notifications demonstrates a monitored system and can also prove useful if elevation of the finding becomes necessary.

Be sure to follow-up on corrective actions from previous audits. Don't only audit to see that corrective actions have been implemented. Make sure the corrective action corrected the problem that caused the corrective action in the first place. ❑

About the Author

Jackelyn Rodriguez has 18 years of experience in all facets of quality assurance. She specializes in international and United States regulations, which encompass quality systems, design control, CE-marking, risk management, medical device reporting, post-market surveillance, and vigilance. She holds a Bachelors of Science degree in Business Management from the University of Phoenix, and is a certified member of the Board of Examiners for the Malcolm Baldrige National Quality Award Program, the Board of Examiners for the Management Systems Provisional Auditor, as well as an examiner for the President's Quality Award Program. Rodriguez currently is Senior Manager, Quality Systems/Regulatory Compliance for Medtronic MiniMed located in California. She can be reached by phone at 818-576-5624, by fax at 818-576-6266 and by e-mail at jackelyn.rodriguez@minimed.com

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Automation Quality Assurance Planning Guide

by ***Robert W. Stotz, Ph.D.***

The automation quality assurance planning approach to validation of computer systems was introduced to Journal of Validation Technology readers in 1994.[1] A subsequent article[2] described a system lifecycle methodology for validation of computer systems utilizing an automation quality assurance planning approach. The following provides guidance in the application of this approach, and the generation and content of an Automation Quality Assurance Plan (AQAP).

An AQAP emphasizes the content, quality, traceability to user requirements, and hierarchy of documentation to be generated during the lifecycle process.

The Food and Drug Administration (FDA) recently defined software validation[3] as: "…confirmation by examination and provision of objective evidence that software specifications conform to user needs and intended uses, and that the particular requirements implemented through software can be consistently fulfilled." Since software is an essential component of a computer system, the term 'computer system' can be substituted for 'software' to provide a definition of computer system validation. Therefore, computer system validation is a lifecycle process, proceeding from concept through engineering design, construction, qualification and/or commissioning, and maintenance of a computer system to its eventual retirement. Throughout the lifecycle, objective evidence, i.e., documentation, must be compiled that confirms that the computer system will consistently conform to its user needs and intended uses. In other words, documentation is the primary focus in the validation process for computer systems.

Therein lies the primary strength of the automation quality assurance planning approach to validation, i.e., its focus on documentation. An AQAP emphasizes the content, quality, traceability to user requirements, and hierarchy of documentation to be generated during the lifecycle process. Another strength of the AQAP approach includes integration of validation activities with overall project-related tasks.

The AQAP approach modularizes a given project into phases, and defines inputs and outputs (deliverables) for each phase. Quality attributes are assigned in the AQAP to the outputs of each phase (the outputs become inputs to the subsequent phase), and "quality barriers" for penetration of deliverables between each phase of the project can also be established. Any non-conformance of a given output to assigned quality attributes are reported as anomalies. It is important to note that an anomaly is an issue that requires further action, and is not to be construed as an error condition. For example, if a required functionality, as defined by the computer system specifications, was found to be missing, an anomaly report would be generated. An anomaly report requires an action to be performed within a specified timeframe before the quality barrier to the next phase can be penetrated. This method of anomaly reporting provides a complete history of all anomalies reported and their resolution during the course of a project. For projects that are already underway or ones involving existing (legacy) systems, development of the AQAP should follow a detailed assessment of available project-related information.

In general, an AQAP can be developed and implemented earlier than a traditional validation project plan, (or project-specific Validation Master Plan, VMP) since many of the particulars required for developing a validation plan are not known until later in the development process. In addition, in the System Lifecycle (SLC) approach using an AQAP, the validation plan can be generated later as an extension of the AQAP. As an extension of the AQAP, the validation plan would assign responsibilities for specific tasks described in the AQAP, describe the methodologies and procedures to be used in accomplishing the validation tasks, and establish a timeline or schedule for completing project tasks.

The methodologies outlined in the following guide are modeled after Institute of Electrical and Electronics Engineers (IEEE) Standards 730-1998 (Standard for Software Quality Assurance Plans) and 730.1-1995 (Guide for Software Quality Assurance Planning), but are not intended to be in rigid compliance with these standards. This guide is intended to supplement project planning and management practices for automation projects, and aid in the development of a project-specific AQAP. Execution of the AQAP will establish confidence that automated equipment and computer systems are validated, and this validated state will be consistently maintained during routine operation.

1.0 Objective

The development, implementation, and maintenance of a computer system in a regulated environment should follow a SLC methodology, such as the one referenced above. The basic requirements of all SLC models are the same, i.e., all models stress good quality engineering practices with adequate checks and balances throughout the SLC. The SLC methodology forms the basis for the project-specific AQAP, supporting the development and implementation of the system.

The complexity and rigor of the validation process, and the level of documentation compiled during the lifecycle, should directly depend on the complexity of the computer system, its potential impact on the product/process being controlled and/or the records being generated/maintained, and the degree of customization. A cost-effective and efficient methodology for determining the appropriate rigor of the validation process and level of documentation to be compiled during that process involves performance of an assessment of the risk associated with each function of a computer system.[4] Assessment of risk is an integral part of the AQAP approach to validation of computer systems.

2.0 Scope

This AQAP guide can be applied to any automation project, including legacy (existing) equipment and systems, system/equipment upgrades, and new systems or equipment being added, or under development. This guide is intended to be applicable to traditional SLC development techniques, but could also be applied to Rapid Application Development (RAD), prototyping, spiral, or other approaches. Automated tools and techniques should be applied as appropriate, following applicable standards, thereby minimizing paper documentation. The management and project team needs to determine the appropriateness of using this guide and incorporate the practices, as necessary. If more extensive guidance or standards have been developed and used by the project team, the group should follow those practices.

3.0 Responsibilities

An AQAP should be prepared for each automation project by a team consisting of members from those departments responsible for development, installation, support, validation, and eventual operation and maintenance of the automated system. Suppliers and external service providers are to be managed according to company-supported programs described in the AQAP that ensure that provided products and services conform to appropriate development standards and practices.

4.0 Procedure

The following plan sections provide minimum requirements for the preparation and content of AQAPs. Additional information for a given section or additional sections may be added as required. Information relevant to a given section that appears in other documents should be referenced. If there is no information pertinent to a given section, then a definitive statement of its non-applicability, together

with justification for the exclusion, should be made in the affected section.

4.1 Front Matter

4.1.1 The plan should have a title page(s) identifying the specific project, date of publication, document number, revision number, project location, and author.

The approvals page should contain areas for printed names and corresponding signatures, and dates for the approvers of the AQAP.

Each major stakeholder in the project should have a management representative responsible for approval of the AQAP and other deliverables generated during project execution. At a minimum, the approvers should include the system owner management, and responsible quality unit for the system.

4.1.2 The publication record or revision history page provides for active tracking of revisions. The revision number, date of the revision, revision author, and a comment section for summarizing changes should be included on this page.

4.1.3 The table of contents page should reference the sections of the AQAP outlined below, and will provide for faster referencing capability, especially in more complicated projects.

4.2 Sections of the AQAP

4.2.1 ***Purpose*** — The purpose provides the overall reason for the plan, stating the major components and intended use of the resulting computer system, portion of the lifecycle covered by the AQAP, and its relationship to corporate policies.

4.2.2 ***Scope*** — The scope states the relationship of the plan to the specific computer system project. It describes the intended use of the plan and the areas it addresses throughout the life of the plan. It should discuss the justification/rationalization required for departures from the plan. If phases are employed (the recommended approach), each phase should be explained separately.

4.2.3 ***Definitions and Acronyms*** — This section defines all terms and acronyms used throughout the AQAP that may be different or unfamiliar to commonly used and understood terms for the development of computer systems. This section may reference professional glossaries for computer system technologies, or other technologies and published lexicons used for site operations. This will establish a common basis of understanding and facilitate communication. Where similar terms coexist having different meanings, the preferred meaning should be identified to eliminate ambiguity.

4.2.4 References to Policies, Standards, Practices, and Guides — This section identifies all policies, standards, practices, and guides to be applied, defines how compliance to these will be monitored and assured, and provides a complete list of all documents used as a reference within the AQAP, and the sources from which they can be obtained. Previously developed policies, standards, practices, and guides approved by corporate and divisional organizations should be used, when appropriate. The application of these to the project should be fully analyzed. Any limitations in the selected policies, standards, practices, and guides should be described. Definitions of needed enhancements should also be described and put into effect prior to using them for the project. If no policies, standards, practices, or guides exist for a specific activity, the project team should define a project procedure for the activity.

4.2.5 Organization, Responsibilities, and Organizational Tasks

4.2.5.1 The organization section describes each major organizational unit that impacts and controls the quality of the system being developed and maintained. The independence or interdependence of these organizational

units, and the delegation of any responsibilities to other organizational units and/or third-party providers should be clearly described.

4.2.5.2 The responsibility section describes responsibilities by organizational unit, and specific tasks for each organizational unit associated with the project.

4.2.5.3 The task section describes the tasks associated with each phase of the project, with emphasis on quality activities and deliverables. The order of tasks should be clearly described. Task descriptions should be complete and unambiguous, noting any variations from policies and standards with full justification for differences. Project plans, tables, graphs, and other pictorial representations may be used whenever possible to illustrate relationships of tasks to the lifecycle and staffing requirements. Documentation and other deliverables associated with each task should be defined as part of the required outcome of each task. Minimum requirements for documentation are described in the system lifecycle methodology guideline.[2]

4.2.6 Reviews and Assessments — This section defines the technical and management reviews and assessments to be conducted throughout the lifecycle. It states how the reviews and assessments are to be conducted. Results of reviews and assessments serve as a basis for management decisions during the development process. Completion of reviews provides assurance that design integrity is maintained, technical deficiencies are corrected, and changes are implemented with minimum impact to the project. A non-project team member should perform reviews and assessments to ensure objectivity. Review and assessment procedures also define follow-up actions to assure that recommendations are properly implemented.

Suggested reviews and assessments include, but are not limited to:

- Functional/Requirement specification reviews
- Design reviews
- Code reviews
- Operation/Maintenance reviews
- User documentation reviews
- Test plan reviews
- Tool and package reviews
- Educational material reviews
- Procedures and standards reviews
- Project plan reviews
- Vendor, physical, and operational assessments

4.2.7 Testing — Testing and evaluation actions are integral parts of development methods, and quality assurance actions guarantee their satisfaction. Testing during the development phase should include unit, integration, system, performance, and acceptance testing. All associated documentation covering scripts, data, and results should also be included. During the maintenance phase, testing is required in association with corrective, adaptive, and perfective maintenance work. A description of maintenance testing for support of the system should be defined. Include other testing required because of business or regulatory concerns that may not be part of the development process. Testing requirements should define the needs, scope, governing documents, and responsibilities.

Testing may include:

- **Interface** – ensuring proper operations with external computer systems
- **Maintenance** – ensuring that software changes perform as expected
- **Backup and recovery methods** – ensuring minimal system interruptions resulting from system failure
- **Manual intervention and operation** – ensuring proper system problem override performance
- **Security** – ensuring integrity and protection of data
- **Safety** – ensuring safe environments for the system and users
- **Acceptance** – ensuring satisfaction of requirements prior to release

4.2.8 Problem Reporting and Corrective Actions — This section defines methods to report, track, and resolve problems. It should define the specific organizational responsibilities for implementation. As problems are found during and after development, it becomes important to assure appropriate attention to resolution throughout the project. Changes encountered during development need to be closely controlled to minimize the effect on subsequent phases. Procedures should be defined to provide an investigative flowpath resulting in timely courses of action.

4.2.9 Tools, Techniques, and Methods — This section identifies special tools, techniques, and methods used that support all aspects of system development and maintenance to assure consistency and quality. It should list or reference those tools, techniques, and methods that are available, as well as those that need to be acquired or developed. Typically, they include utilities, testing aids, documentation aids, file comparators, analyzers, simulators, performance monitors, and any industry-adopted standards for inspections, reliability measurements, and verifications of designs.

4.2.10 Configuration Management *(See Figure 1)* — This section defines methods used to identify system elements for the purpose of controlling, implementing, and tracking changes, and monitoring releases. This includes change management and change control, and version control practices that govern hardware, software, and documentation changes for corrective, adaptive, and perfective changes during execution of the AQAP. Coverage includes development and maintenance of the system. Because of the complexity of some projects, a configuration management method for reporting, analyzing, tracking, and follow-up is required to determine the source of corrective measures. Variations and limitations of existing practices should be described and fully justified. Management of documentation should be automated whenever possible.

Requirements for configuration management include:

• Assurance that problem reports and proposed corrective actions are analyzed, documented, and corrected by the project team during the development process. The results of these activities must be communicated to all affected parties.

• Assurance that all data used for measuring and predicting software quality and determining the appropriate baseline are updated.

• Assurance of readiness of releases for the operations area.

• Monitoring operational use of the system in its normal operating environment.

Note: Until the computer system is released for routine use, the responsibility for configuration management must reside with the project team. Attempts at implementing or adapting a corporate change control program to managing changes prior to system release seldom, if ever, prove successful.

4.2.11 Records Collection, Maintenance, and Retention — This section identifies documentation that should be retained in accordance with approved schedules. It states the methods and facilities to be used to assemble, safeguard, and maintain this documentation. It includes all applicable schedules for retention. As these records are important for maintenance and regulatory reasons, variations and exceptions to defined practices should be described with full justification.

Documentation that should be controlled includes:

- Development records and documents
- Maintenance records and documents
- Review/Assessment reports
- Training records
- Software source code versions

4.2.12 Training — This section defines the training requirements necessary to meet the needs of the AQAP for development, use, mainte-

Figure 1

Configuration Management: IEEE Standard 729-1983 defines configuration management as a formal engineering discipline that provides methods and tools to identify and control software, hardware, and related documentation throughout its development and use. In other words, configuration management is a lifecycle process for identifying and controlling changes to all the components of a computer system, including documentation.

There are two primary elements of configuration management; change management and change control. Change management is initiated at the beginning of the development process, and is eventually superseded by change control at a defined point in the lifecycle, i.e., design freeze. Design freeze is simply an agreement among all involved parties that no further changes to a design document, system, or system software will be made without the use of a change control procedure. The purpose of a design freeze is to prevent the testing/qualification of an evolving system or its software, and to ensure that system documentation is directly tied to the as-built system.

Change management is a less formal, but structured, method of monitoring changes to design documents and software involving, in the following order, implementation, recording, and periodic peer review and sign-off of changes. The primary purpose of the evaluation process during change management is to provide assurance that changes meet user requirements, and affected design documentation is updated. Change management is primarily the vendor's/developer's responsibility, subject to review and approval by the system owner.

Change control requires, except for emergency changes, evaluation of the change(s) prior to implementation. The primary purpose of the evaluation process during change control is to provide assurance that the change(s) will not adversely affect the performance of the system, all affected documents are updated, and appropriate retesting is performed and documented. Depending on the complexity of the project, two or more change control procedures may be implemented during the lifecycle; the last one being the corporate change control procedure implemented upon the system owner's acceptance of the system for routine use.

For more complex projects, it has proved prudent to implement two different types of change control prior to system acceptance, viz., developmental and pre-acceptance change control. The developmental change control procedure is implemented upon design freeze. This point in the lifecycle is generally where design documents are complete, or nearly complete, and hardware and operating system software are being installed and tested. Changes controlled by developmental change control are generally confined to a specific platform (e.g., Distributed Control System (DCS), Enterprise Resource Planning (ERP), Building Administration System (BAS), or Embedded System) or platform module, and affect a limited number of design documents.

Pre-acceptance change control is implemented at the point where application-specific software is loaded on the installed system, and prior to commencement of integration testing and execution of Operational Qualification (OQ) protocols. Changes controlled by pre-acceptance change control can often affect several modules of the total system, or in some cases, the entire system. Pre-acceptance change control remains in force until system acceptance.

nance, quality, and operational activities. It is advisable to include training plans and schedules that are aligned with appropriate development schedules and activities. End user training schedules should be aligned with the completion of user manuals to aid in creating effective SOPs to support the end use of the system. An assessment of the required skill sets of quality assurance personnel should include knowledge of special tools, techniques, and methods used, and prescribed computing knowledge. An assessment of operational training will assure that the computer system will not be used for unintended operations, and ensure that an understanding of its limitations will be established. If a training plan for the project is currently documented, this section needs only to reference it.

4.2.13 Risk Assessment and Documentation Requirements — The level of validation documentation and testing required for an automated system should be dependent upon the complexity of the automated system. The documentation requirements should be determined using a system risk assessment of the critical functions of the computer system.[4,5]

4.2.14 Security — This section describes the application of corporate and divisional policies on security issues related to the system, its development, maintenance, operation, and use. It includes, but should not be limited to, security from loss, theft, alteration, misuse of company data in computer environments, and misuse of company computer assets. Variations and exceptions to defined practices for security controls should be described with full justification.

4.2.15 Operating Manuals — This section describes the required operating manuals or help facilities for users and support personnel. The descriptions should also include schedules for development and delivery to coincide with system development, testing, and training plans. The operating manuals should follow standards set by the project team. The manuals should reuse available system information, and be stored electronically, whenever possible.

4.2.16 Operating Procedures — This section describes the required operating procedures for operational use. The descriptions should also include schedules for development and approval to coincide with system release and acceptance. End users should develop the SOPs in conjunction with user manual development to ensure agreement between the system use, business process, and system purpose definition. Maintenance procedures should be developed similarly by the maintenance organization, with further attention to the reuse of existing maintenance procedures, whenever possible.

4.2.17 System Performance and Revalidation — This section describes the monitoring of system performance throughout its operational life. It describes the predetermined benchmark criteria used to determine the functionality and performance efficiency. The monitoring practices should be complete with evaluation schedules, responsibilities, and required management reports.

Performance monitoring should review:

- Maintenance work
- Atypical operations
- Security anomalies
- Hardware performance degradation
- Usage errors

The revalidation discussion should describe the maintenance controls used to avert revalidation, and the verification process for these controls. The verification process should emphasize the performance measurements and adherence to performance criteria. The outcome of performance measurement activities should determine the scope of investigative work and revalidation actions. Revalidation triggers should be clearly defined and linked to significant deviations from benchmark criteria, appropriate to the criticality of the system.

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About the Author

Dr. Robert Stotz has more than 24 years experience in the pharmaceutical and healthcare industry, and is Vice President of the East Coast Office of Validation Technologies, Inc. (VTI) located in Exton, Pennsylvania. Dr. Stotz accumulated more than 11 years experience at The Upjohn Company, culminating as Validation Manager for Upjohn's worldwide validation efforts. He spent nearly ten years in the validation services industry before joining VTI in July, 2000. Dr. Stotz works with many multi-national pharmaceutical and healthcare manufacturers in all aspects of operations (particularly computer systems) and validation, from concept through to system/facility qualification and start-up. He has been actively involved with validation issues for more than twenty-three years, and was a member of the Pharmaceutical Research and Manufacturers of America's (PhRMA's, formerly PMA's) Computer Systems Validation Committee for several years. He was also a member of the PDA's Computer Validation Committee that published PDA Technical Report No. 18 on "Validation of Computer-Related Systems," and has presented and published several papers on the subject of validation. Dr. Stotz holds a Ph.D. from the University of Florida, B.S. and M.S. degrees from the University of Toledo, and during his career has taught at several universities. He can be reached by phone at 888-330-8978, by fax at 610-594-0916, and by E-mail at Roberts@validation.org.

Article Acronym Listing

AQAP:	Automation Quality Assurance Plan
BAS:	Building Administration System
DCS:	Distributed Control System
ERP:	Enterprise Resource Planning
FDA:	Food and Drug Administration
IEEE:	Institute of Electrical and Electronics Engineers
OQ:	Operational Qualification
SLC:	System Lifecycle
VMP:	Validation Master Plan

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Using Gap Analysis to Identify Systematic Quality Problems

The FDA's inspection will not identify all deficiencies and problems, and will not necessarily determine the real cause of systemic problems.

by
Rebecca Fuller Hyde
President
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Many of the techniques and methods for gap analysis that are described in this article are equally applicable to a traditional quality audit. The principles for conducting effective interviews and record reviews are the same, regardless of the audit approach.

Introduction

Internal audits are an essential part of a Quality Assurance (QA) program, and a regulatory requirement for drug and device manufacturers. But when they are not effective, either because auditors are not finding the deficiencies, or the audit results are not eliciting appropriate corrective action, it is likely that the Food and Drug Administration (FDA) will uncover the problems during their inspection.

In a recent case, the FDA inspected a small medical device company that had conducted three recalls in an 18-month period. The result was an FD-483 listing several quality system deficiencies and a Warning Letter. The company sent a short response letter listing corrective actions to address the seven items on the 483, and thought that would be the end of it. The FDA compliance officer reviewing the case sent another letter asking several more questions and requesting more documentation. This began a long series of correspondence lasting over six months, during which the FDA repeatedly stated concern regarding potential quality problems, and the company continued to respond by answering only the specific questions asked by the FDA. After six months of on-going written dialogue, both the company and the FDA were frustrated; the FDA not hearing what they wanted to hear, and the company not understanding why the FDA still was not satisfied with their responses. In one of the later letters, FDA informed the company that they must perform an independent and complete internal audit of their quality system, and assure that corrective actions were implemented systemically. What the FDA wanted, and what the company had failed to do, was take accountability for finding the systemic quality issues and correcting them.

The FDA's inspection will not identify all deficiencies and problems, and will not necessarily determine the real cause of systemic problems. Simply correcting what the inspector documents on their list of observations, (the FD-483,) is often inadequate, and is one of the common mistakes made by companies who do not have experience responding to a FD-483 or Warn-

Figure 1

When is a Problem Systemic?

A Problem is systemic when if affects or can be seen in multiple product types, product batches, types of equipment, departments, or procedures. A systemic problem may be indicated by a rash or trend in errors, deficiencies, or events over a period of time.

It is *not* an intermittent problem or isolated error.

ing Letter.

An important consideration in responding to a Warning Letter includes taking accountability for finding all of the deficiencies, and making corrections on a systemic level. You may be hearing frequent references to the term "Gap Analysis" within FDA-regulated industry, since companies under enforcement action are commonly using gap analysis techniques to try to identify all of their compliance problems, both intermittent and systemic. Gap analysis is the common (and necessary) first step of a response to address a Warning Letter or enforcement action. Why a gap analysis? It goes beyond the scope of routine internal audits, which, depending on the extent of deficiencies identified during the FDA inspection, have not necessarily been effective.

There are several ways that a gap analysis can be used to improve a quality system. This article will compare gap analysis techniques to those of a traditional audit, explain the benefits of gap analysis, and provide guidance on the preparation and performance of a gap analysis.

What is a Gap Analysis?

In a typical audit, a sample of information and data is reviewed, and observations are made, to determine if procedures are adequate and are followed, if regulations are followed, and if deficiencies are being identified and corrected. Given that the system being audited is in control and the audits are effective, the audits will typically find intermittent examples of non-compliance or procedural errors so these can be corrected.

When internal audit results, an FDA inspection, or quality metrics analyzed as part of a Corrective and Preventative Action (CAPA) program demonstrates evidence that part of the quality system, a process, or product is not adequate, it may be necessary to conduct a very detailed analysis of the non-compliant area to determine the extent and root cause of the problem, and what will be necessary to correct and prevent the problem on a systemic level. Depending on the nature of the problem, a gap analysis can provide a useful tool for examining, in much greater detail than a traditional audit, every aspect of the problem area (procedures, records, personnel, resources, management, and effectivity) so that an appropriate, thorough, and systemic corrective action can be initiated.

For example, if an internal audit finds that a "thermometer used to monitor the water bath temperature was not calibrated," the typical corrective action would be to remove the thermometer from service, calibrate it per procedure, and evaluate the degree of risk to the product caused by this deficiency. But if an audit (or a series of audits) finds several pieces of equipment were not calibrated, there is a systemic problem. In this case, a gap analysis of the entire calibration program would help identify the root cause of the problem, which could be, for example, procedural deficiencies or training problems. The gap analysis would involve a very in-depth review of all equipment records and a physical inventory of every piece of equipment to identify exactly which pieces of equipment are affected. It would include an assessment of all of the calibration procedures, software programs used to manage calibration schedules, calibration training program, and a determination of when the program failures first occurred, so that a risk analysis can be conducted to evaluate how this may have affected a potentially large population of product lots.

The application of gap analysis is not limited to response to audits or inspections; it can be a useful and proactive tool for implementing compliance with a new industry standard/new guidance document. A gap analysis is helpful when a company is trying to bring themselves into compliance with a regulation that they were not previously meeting. For example, companies preparing to comply with Title 21 Code of Federal Regulations (CFR) Part 11, Electronic Records and Signatures, will often use gap analysis techniques to identify what tasks need to be done in order to fill the gaps between current operations and the regulatory requirements. A Part 11 gap analysis will typically begin by making a complete inventory of all software and documenting its intended use and current configuration. Each software program and computerized system would be analyzed against defined requirements, such as proper control of passwords, audit trails, and validation.

Once this analysis is complete, a remediation plan can be developed to bring systems into com-

pliance and implement procedural controls. The remediation plan documents the corrective action, timelines, responsibilities, and resource allocations for corrective actions. It is important that progress toward completion of remediation plans or corrective action plans is monitored, documented, and that failure to meet objectives or deadlines are addressed by management.

Audit Versus Gap Analysis

A quality audit is an independent review conducted to compare some aspect of performance with a standard for the performance. A gap analysis attempts to identify gaps between a pre-defined standard or goal, and the actual program, operation, or system in use. Both an internal quality audit and a gap analysis look for evidence of quality or compliance deficiencies. On the surface, a gap analysis doesn't sound much different than a quality audit, and, at its core, the gap analysis is an audit.

Both need to be conducted by individuals who are independent of the area being examined, both include the documentation of results, and both result in corrective actions that are managed through the company's CAPA program. But, there are specific differences between a gap analysis and audit that often make a gap analysis more effective than a traditional internal audit.

A company's internal auditors, particularly those new to auditing, tend to focus on whether or not the company is following their procedures. It is less common for internal auditors to evaluate whether or not the procedures themselves are appropriate. In a gap analysis, management agrees on a scope for the analysis, and a set of standards and expectations that the company wants to meet, typically going beyond whether or not the procedures, as written, are simply being followed. For example, in a gap analysis of a software QA program, the company may determine that in addition to meeting requirements of FDA regulations and pre-defined list of FDA guidance documents, they will also benchmark and document gaps between their current software development program and the Institute of Electrical and Electronics Engineers (IEEE) standards and the National Institute of Standards and Technology (NIST) standards for software development, verification, and validation.

A gap analysis will identify areas or operations that can be improved to meet current industry standards, or a defined group of "best practices," regardless of whether or not failing to meet these standards presents a potential for non-compliance or product defects. This can help assure best use of resources and operational efficiency, as well as product quality and risk management.

A gap analysis is highly focused on one specific process or program, examining all aspects of the program, and typically a greater number of records than might be examined in a typical internal audit. The amount of time necessary to conduct an internal audit depends on the number of products, complexity, size of the organization, and extent of the programs. In a small-to-medium size medical device manufacturer, an internal audit may cover many aspects of the quality system in one or two weeks, but a gap analysis may take the same amount of time; concentrating on a single part of the quality system. If a part of the quality system is not adequate or is not in control, it takes time to identify the scope of the problem, so that the most appropriate corrective action can be determined.

All audits should review an appropriate statistical sample of records. But when a statistical sample of records is reviewed in a traditional quality audit covering, for example, design controls for four different product families, the auditor might look at one of the four design history files to assess compliance. During a design control gap analysis, three or even all four design history files might be reviewed to determine if a problem with one file is also apparent in the others (i.e., the deficiency is systemic and not isolated to one file). This will help determine the scope of corrective action that may be necessary to fix a systemic versus an intermittent problem.

The most important reason that a gap analysis is an effective tool for identifying real problems, their root causes, and the best corrective action is the approach, which is much different that that of a traditional quality audit. The interaction and rapport between the analyst and the personnel in the area being reviewed is often more collaborative and open than during an audit. Just the use of the term "audit" brings to mind menacing encounters with the Internal Revenue Service (IRS). While everyone will agree that audits should never be antagonistic, those who are audited still may find the experience similar to being judged before a court where the precept of "innocent until proven guilty" may or may not be in force. No one wants to be audited. If you were a department supervisor who just went through a stressful FDA inspection that identified several deficiencies, which would you rather hear from the head of Regulatory Affairs?

"As a result of the recent inspection, we are coming in to perform a more thorough audit of your area."

or

"In response to the recent inspection, we would like you to participate in a gap analysis of your area. We want to understand all the issues and determine what improvements we should make."

In an audit or FDA inspection, the persons being interviewed are often trained to answer only the question asked, and not offer any unsolicited information. The "survival instinct" kicks in, and the persons being audited will try to prevent problems from being identified as a means of self preservation ("If they see I made a mistake, I might be fired."). A gap analysis should begin by ensuring that everyone involved understands that in order to get the maximum out of the process, open and honest information sharing is imperative, and will not result in retribution. The participants need to know why the gap analysis is being performed, what the objectives are, and how they can help meet these objectives. They need to trust the person(s) conducting the gap analysis, and understand that the objective of the process is not to identify "who did what wrong," but rather, what are the procedural, training, resource, and management needs to prevent the reoccurrence of errors, or improve the process.

Preparing for a Gap Analysis

In order for a gap analysis to be successful, management must agree in advance on the scope, as well as the specific standards/requirements or benchmarks to be met. The analysis needs to be focused on a specific area, so that it is sufficiently detailed. Defining what will and won't be covered in the gap analysis is more difficult than it may seem, since all elements of the quality system link together, and are often closely related. For example, a gap analysis covering product and process controls would evaluate:

- Process control procedures
- Deviations
- Equipment
- Environmental controls
- Personnel
- Buildings
- Control of manufacturing materials (charge in of component, time limits on manufacturer)
- Yield reprocessing/rework
- Automated process controls
- Process validation, and
- Process monitoring

And depending on the product types involved, a process control gap analysis could easily extend to many supporting systems and related programs or operations, such as:

- Software control, development, verification, and validation
- Change control
- Part 11 compliance
- Training

A complete gap analysis of production and process controls might have to cover very specific validation requirements, such as those for:

- Sterilization validation
- Cleaning validation
- Lyophilization,
- Process water (Water-For-Injection [WFI], Purified water, etc.)
- Analytical method validation

The records associated with all of these programs and processes could easily fill a room, and an in-depth gap analysis covering all of the issues listed above would take a great deal of time and resources. In order to complete the gap analysis, it is important to define and limit the scope, but at the same time, assure the scope is not so narrow that systemic issues won't be identified. In the case that an internal audit found several problems with a operation of a lyophilizer, the objective of a gap analysis might be to identify all quality system deficiencies related to lyophilization processes extending to equipment control, process validation, automated software controls, operator training, and related procedures for these activities.

It may be helpful to develop a gap analysis plan to formally document the scope. Keep in mind that it may be just as important to document what *will not* be covered, as what *will* be covered during the gap analysis.

In order to get the scope under control, management must agree on the objective to be met, and the standards or "best practices" to evaluate against.

What regulations must be met? What specific guidance documents or technical guides will be used to establish requirements to be met in the gap analysis? What standards will be met (such as International Organization for Standardization [ISO] or American National Standards Institute [ANSI])? Are there corporate policies that must be met? Current industry practice that will be applied? Benchmarks?

Once the objectives and scope are determined, one final decision is whether or not to use a gap analysis worksheet or matrix to document results against specific individual requirements.

Matrix or No Matrix

Rather than using a standard checklist, a gap analysis matrix or worksheet is a tool for organizing information and document results. A worksheet makes it easy to document results of the analysis and review results (refer to *Figure 2*). The specific discrete requirements that the company wants to meet are specified, and actual results of the analysis are recorded next to each requirement. In addition to the requirement and the results, the worksheet might also include:

- Bibliographic reference to the regulation, guidance, document, article, corporate policy, or other document from which each requirement was derived.
- Cross reference to the specific records reviewed during the analysis
- Decision regarding the extent to which the requirement was met, and
- A scoring system to quantify the result of the analysis (such as percent of defined requirements met or not met.)

Once all the requirements are compiled in the worksheet or matrix, it should be reviewed and approved by management to assure everyone concurs with the individual requirements or industry practice to be applied. When developing an extensive worksheet, it is helpful to break the worksheet into subpart or sections. For example, the sections for a process validation gap analysis would include: Installation Qualification (IQ), Operational Qualification (OQ), Performance Qualification (PQ), process monitoring, automated process controls, and training. Within each of these subsections, the procedural, implementation, and documentation requirements would be listed.

Figure 2

GAP Worksheet for *(Program/System)*
Part 1 – General (Policies, Procedures, Management, and Planning)

Item	Requirement	Reference[1]	Documents Reviewed	Observations Comments	Assessment
1.	*Example A*: Validation policies or proce–dures explain or provide criteria for determining what processes are to be validated. (should be based on risk assessment methods)	1	xx-xxx-xxx,		❑ Meets Requirement ❑ Does not Meet Requirement ❑ Requirement Met, but improvement needed. ❑ NA
2.	*Example B*: Documented procedures provide a mechanism for the approval and release of equipment and processes. Procedures provide instructions for identifying equipment that is not approved to prevent its unintentional use in production.	3, 4			❑ Meets Requirement ❑ Does not Meet Requirement ❑ Requirement Met, but improvement needed. ❑ NA
3.	*Etc…*				❑ Meets Requirement ❑ Does not Meet Requirement ❑ Requirement Met, but improvement needed. ❑ NA

1. Numbers would correspond to numbered references in the bibliography attached.

The downside is that creating a complete worksheet of individual discrete requirements is resource intensive and very time consuming. Developing a thorough worksheet requires line-by-line review of every standard, corporate reference document, regulation to be met, and may actually take longer than performing the gap analysis. It may be a good investment, since once it has been developed, it can be used for many future analyses, including those of suppliers or other divisions of company.

Unfortunately, if a gap analysis must be done under tight time constraints in response to a Warning Letter or FDA enforcement action, it may be necessary to define the regulations, guidelines, and standards to be met, and trust the person(s) executing the analysis to evaluate effectively against these criterion, without compiling each discrete requirement in a matrix. The gap analysis results would then be documented in a detailed report, rather than on the worksheet or matrix.

The persons conducting the gap analysis must have a higher degree of audit skills and experience if a pre-defined worksheet or matrix of requirements is not going to be used. Of course, using a worksheet is a good idea and if one exists, use it. If one doesn't exist, is important to weight the benefits of developing a worksheet against resources and time constraints.

During the Gap Analysis

Those participating will need to share their opinions and concerns to assure that all the problems are identified. The exercise should be a positive learning experience for everyone, and no one should feel defensive.

Executing the gap analysis simply requires comparing the current system, its supporting documentation, and the personnel/resources against the defined requirements. To determine if requirements have been met…

- Read documentation
- Examine a sufficient number of records to determine whether or not an observed deficiency is systemic or an isolated incident or error.
- Ask questions. Try to get the employees involved by listening to what they think. (See *Figure 3*.)
- Use your instincts
- Once you have determined that a requirement has not been met, move on
- Get out of the conference room and onto the manufacturing floor

Figure 3

General Questions to Ask When Determining Effective Procedures

- What is the purpose of the (task/process) you are performing?
- How were you trained to perform this task?
- What is the most difficult aspect of this task?
- What is the (scrap/defect/failure) rate?
- How often is this (process/equipment/line) down due to problems or for repair?
- Where is the procedure or instruction for performing this task?
- Do you follow these procedures or instructions?
- Do you perform this (process/task) the same way each time you do it?
- How do you record that you performed this task?
- Was this (task/process/equipment/software) changed anytime recently?
- Do you think this process should be changed or improved?
- How would you change or improve this process?
- If this (process/task/test) were performed incorrectly or did not work, how would it affect the product?
- If you observe a problem with the (equipment/process/the way personnel perform a task), how would you handle that?

When a problem is identified, try to determine its cause. Identify if the problem affects multiple product lines, multiple batches, or multiple operational areas (i.e., is the problem systemic)? Is there an underlying training or resource issue? Are the procedures poorly written?

When determining if a requirement has been met, there are three general conditions you must determine:

❶ Do the policies, procedures, forms, and templates meet the defined requirements? (Establishment)
❷ Have the requirements been met in actual practice? (Implementation)
❸ Are resources, training, and review adequate to support the requirement, continue to be met? (Management)

❶ Policies and Procedures

Determine what has been established procedurally in comparison to the requirement. Look for any inconsistency or conflicting requirements in procedures, and assure that cross reference to links to other necessary procedures are made. Assure that

definitions are consistent with those in the regulations or standards being applied. And, most importantly, determine if the procedure is clear, and can be understood by the persons who will be using it.

❷ Implementation of Procedures

Assure that procedures have been effectively implemented by reviewing records, reports, examples, etc. Determine a plan for sampling records and reasonable sample size to review in order to assure that systemic problems will be identified. Sample size should take into consideration the risk of the product or process being reviewed. It is often necessary to review more records than would be reviewed during a routine audit in order to understand the extent and cause of the problem. Once the extent of a problem is known and corrective actions are evident, don't continue to review records and examples. It is not necessary to develop an arsenal of "evidence" to support an observation or deficiency. Once the analyst and department manager agree that there is a problem and everyone understands the extent of the problem, move on to the next issue. When applying the Quality System Inspection Technique (QSIT), FDA uses binomial staged sampling plans to help determine the number of records to be reviewed. The investigator may select either a 95 percent or 99 percent confidence level. Tables, such as the binomial sample plan tables in the FDA's *Guide to Quality System Inspection Technique,*[1] may be useful.

❸ Management of the Process or Program

Evaluate whether or not qualified personnel, tools, skills, and technology are applied to the task or operation being analyzed. (This is an aspect that may not be evaluated during a routine internal quality audit.) The effectiveness of the training program is ae efficient indicator of how management supports the quality system. Training requires resources and commitment. Determine if employees understand the terminology in their procedures, and whether they apply it correctly during conversation. Do employees have knowledge of the product, process, task, or equipment operation?

Using Statistical Analysis During a GAP Analysis

A gap analysis may include the use of several statistical tools to analyze quality data. Effective data analysis helps identify problems, prioritize necessary corrective actions, and allocate resources appropriately. The analysis done during a gap analysis might augment or expand upon analysis already being performed as part of the CAPA program. Typically, a CAPA program will include trend analysis of complaints, rework rates, product or batch failures, scrap rates, non-conforming materials, corrective actions, service/repair data, and Out-of-Specification (OOS) events, just to name a few. Consider the example where a routine OOS trend analysis reviewed during a monthly CAPA meeting showed an increasing frequency in OOS events over time. A gap analysis of analytical lab operations might be initiated as follow-up. During this gap analysis, OOS data might be analyzed in several different ways to determine the most likely cause of the increased OOS rate. The analysis will be more detail than what is routinely performed as part of CAPA. The analyst will "drill down" into the data in order to better understand the factors contributing to the increased OOS rate identified through the CAPA program.

There are many analysis techniques. The two most commonly used (and easiest) are described below with examples:

- *Pareto Analysis* – can help identify which failure modes or defect types occur the most frequently. The Pareto principle states that a few contributors are responsible for the majority of problems. A Pareto analysis summarizes facts in a form that shows where most of the problem is concentrated.

Figure 4 is an example of a pareto chart showing the major contributing causes of OOS events in an analytical laboratory.

- *Frequency Distribution Histograms* – show dispersion along a scale of measurement, and relates the frequency of occurrence of the various values. Refer to *Figure 5*.

After the Gap Analysis

The results of the gap analysis will be documented in a final report attaching any worksheet or matrix used. The final report should be objective, and provide any necessary explanation of the observations, recommended corrections, or suggestions for improvement. The suggested corrective actions and recommendations must be commensurate with the significance and risk of the problem.

It may be helpful to provide an executive summary. The summary should not be more than one page, and provide a brief summary of findings, high-

Figure 4

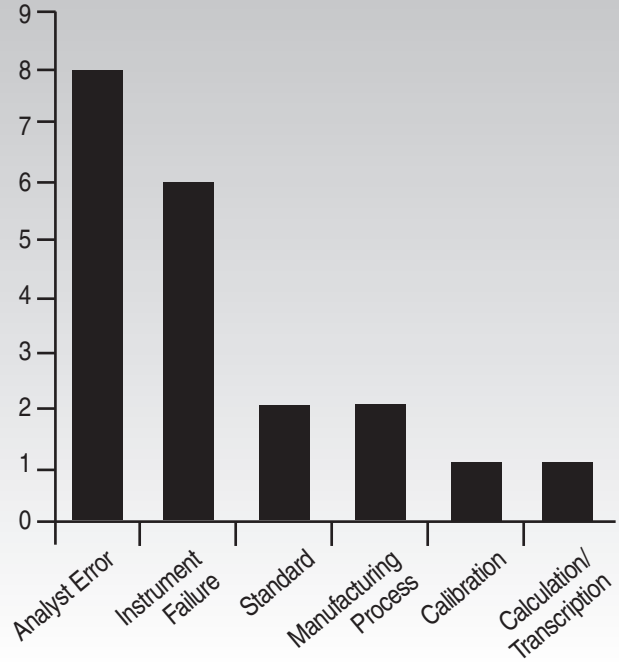
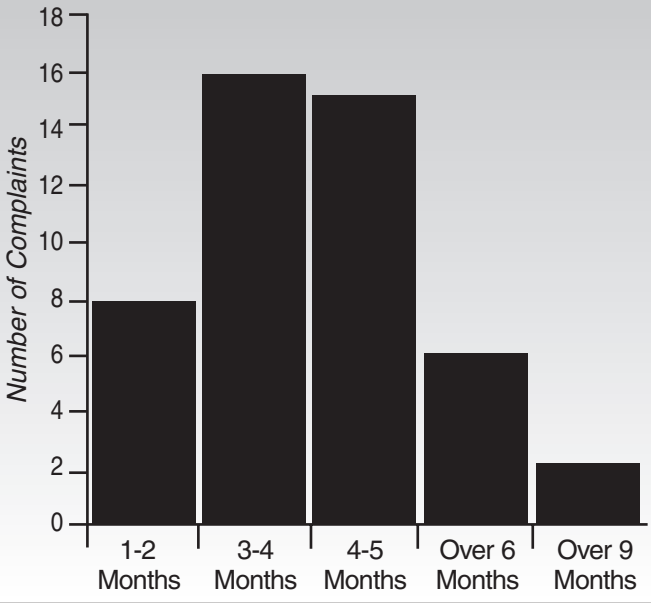


Figure 5



lighting any major issues or problems. The summary should discuss the business, compliance, or product safety risks that may exist, based on the results of gap analysis. It should explain the extent and significance of the problems identified.

Assigning Quantitative Results

Assigning quantitative results of the analysis is not necessary, but may be a helpful method to track progress. The gap analysis would be executed to identify problems, and then a score could be assigned (e.g., 65 percent of requirements met). Following corrective action, the gap analysis would be repeated. The new score would be compared to the old score, and this process would be repeated until 100 percent of the stated requirements were met. Metric or quantitative results are only practical if a worksheet or matrix is used to execute the gap analysis.

Scoring methods can be easy or complex. The simplest scoring method would assign the same weight or significance to each requirement, and determine the percent of requirement met or not met. In a more complex scoring system, each requirement would be assigned a weight. See *Figure 6*.

Figure 6

Scoring System

Classification of Defect or Quality Problem	Explanation	Weight (Points)
Critical	A requirement or objective that, if not met, would likely result in a product defect that could cause injury or death.	3
Major	A requirement or objective that, if not met, would cause a product defect or noncompliance with federal regulations.	2
Minor	A requirement or objective that the company wants to meet for efficiency, business, or other reasons.	1

The gap analysis worksheet or matrix would stipulate the weight, and the total points possible would then be calculated. The quantitative results would be expressed as a total number of points achieved, and a percentage of total possible points.

The metric results of the audit would be summarized in the report as shown in *Figure 7*.

Conclusion

Standard language in a Warning Letter typically includes the statement that: *"The identified deviations are not intended to be an all inclusive list of*

Figure 7

Audit Metric Results

Number of Requirements Specified: 200 (Total Number of Items not Marked "NA")		
Requirement Fully Met:	120	60%
Requirement Not Met:	55	28%
Requirement Met, Improvement Needed	25	12%

deficiencies at your facility. It is your responsibility to assure that your establishment is in compliance with all requirements of the federal regulations." The FDA makes their position clear: their inspectors are not your internal auditors.

When conducted effectively, audits play an important role in quality assurance. However, if the FDA finds problems, it is likely because your routine internal auditing program is not identifying problems, nor eliciting the appropriate corrective actions. It may be necessary to go beyond the traditional internal audit, and allocate additional resources for conducting a thorough gap analysis of one or more areas of the quality system. This will identify all deficiencies or "gaps," so that they can be corrected on a systemic level. FDA expects Industry to take accountability for identifying the root cause of quality problems, and take appropriate actions to correct these problems and prevent their reoccurrence. Once the major systemic problems have been identified and corrected, routine quality audits, if managed and conducted effectively, will help maintain the quality system. ❑

A template of a gap analysis report is provided on the following pages.

Gap Analysis "Do" and "Don'ts"

Gap Analyst:	Analyzed Employees:
• Do prepare. Know the objectives and scope. • Do be objective, but thorough. • Do get opinions and ideas from the employee in the affected areas. • Don't stray beyond the scope. • Don't be judgmental. • Don't focus on listing errors or defects, but determine why the errors or defects occurred.	• Do communicate problems or quality issues that you know about to the analyst, so they can be recorded and corrected. • Do provide open and honest answers. • Don't be defensive. • Don't place blame.

About the Author

Rebecca Fuller Hyde has combined experience in both government service and private industry, having served as both an FDA investigator and director of regulatory and QA functions for medical device manufacturers. She is the author of the Design Control Implementation Guide, a comprehensive guidance manual published by the ***Institute of Validation Technology****. Ms. Hyde is an active member of the Editorial Advisory Board for the* Journal of GXP Compliance*. She can be reached through her consulting firm, BioAssist, 425-413-9063, or by e-mail at biocom@nwlink.com.*

Reference

1. FDA. *Guide to Quality System Inspection Technique* August, 1999.

Article Acronym Listing

ANSI:	American National Standards Institute
CAPA:	Corrective and Preventative Action
CFR:	Code of Federal Regulations
FDA:	Food and Drug Administration
IEEE:	Institute of Electrical and Electronics Engineers
IQ:	Installation Qualification
IRS:	Internal Revenue Service
ISO:	International Organization for Standardization
NIST:	National Institute of Standards and Technology
OOS:	Out-of-Specification
OQ:	Operational Qualification
PQ:	Performance Qualification
QA:	Quality Assurance
QSIT:	Quality System Inspection Technique
WFI:	Water-For-Injection

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Conducting a Comprehensive Remediation Analysis for Part 11 Compliance

The document control aspect of Part 11 compliance ensures audit trails and retrieval of archived data, and provides fodder for new engagements in research.

by
Mark Kropp, MD
Validation Analyst
Pfizer, Inc.

Here the name of the game is remediation for compliance. The Part 11 requirement has not changed, however, its interpretation and enforcement has in light of the new Food and Drug Administration (FDA) guidance document.[1] For us, what was begun, is now being completed. A task force was assembled in order to create a matrix to apply the legislation created and passed in 1997 to those systems being utilized in an FDA-regulated environment. My group focused mostly on computer systems and applications in the laboratory. Coincidently, this included Agilent Technologies and the knowledge engineering management tool called CyberLab. The choice of long-term archiving remained an in-house custom-designed Analytical Laboratory Computer Networking (ALCN), program, ChemStore or CyberLab.

In order to achieve compliance, the regulation was interpreted, and a set of remediation questions were created (refer to *Figure 1*). A Part 11 assessment was performed on current systems. A gap analysis was done. Validation was developed, including a system lifecycle plan, and tests were executed on new systems. Procedural and technical controls mandated by Part 11 were implemented. The major points addressed were security, audit trail, archiving, and retrieval. Training was reinforced consistently and repeatedly.

The remediation plan needed to first address the interpretation of the law. The components of the project followed the seven rules for Part 11 compliance:

❶ Validate
❷ Control system access
❸ Create an audit trail
❹ Check authority and system
❺ Provide accurate and complete copies
❻ Protect system and records
❼ Train adequately

Remediation Approach

Next, a remediation approach was written and a gap analysis performed, along with identification of a procedural (P) or technical (T) solution. The chart appeared much like the one shown in *Figure 2*.

Quality Task Matrix

Next, a quality task matrix was written, along with identification of deliverables. The chart appeared much like the one shown in *Figure 3*.

Figure 1

Part 11 Remediation Analysis Questions

1. Does a requirement specification exist?
2. Does a design document exist?
3. Does testing documentation exist?
4. Does an operating procedure exist?
5. Does a system development lifecycle exist?
6. Does a validation plan exist?
7. Does a validation report exist?
8. Does training documentation exist?
9. Does a change control procedure exist?
10. Is there evidence that data conversion exists?
11. Does a support plan exist?
12. Has a vendor audit been performed?
13. Are all records available for *viewing*?
14. Are all records available for *copying*?
15. Are all records available for *inspection*?
16. Does a procedure for providing records exist?
17. Does test evidence exist to demonstrate record availability?
18. Can records be deleted?
19. Are records proven to be accurate?
20. Are records retrievable?
21. Has a capacity analysis been performed?
22. Does an electronic records retention policy exist?
23. Does backup/restore procedures exist?
24. Do archive/recovery procedures exist?
25. Does a disaster recovery procedure exist?
26. Is virus protection installed on the Personal Computer (PC)?
27. Is virus protection installed on the server? (if applicable)
28. Does test evidence exist to demonstrate accurate and timely retrieval of records?
29. Do controls limiting system access exist?
30. Does a historical users list exist?
31. Does an account management procedure exist?
32. Does test evidence exist to demonstrate system access is limited?
33. Does a secure, non-editable audit trail exist?
34. Is there a computer-generated audit trail?
35. Is there a secure, computer-generated time stamped audit trail that independently records the date and time?
36. Does the audit trail document the operator's entries and actions that create, modify, or delete electronic records?
37. Does the audit trail retain previous values, and are those previous values available for viewing?
38. Is the audit trail retained as long as the electronic record?
39. Is the audit trail available for review and copying at the request of the FDA?
40. Are the system administrator functions included in the audit trail?
41. Is the time source obtained from a secure location?
42. Are controls in place to manage the Data Base Administrator's (DBA) responsibilities?
43. Does test evidence exist to demonstrate the functionality of the audit trail?
44. Are sequences built in and enforced?
45. Are sequences documented?

(Continued)

Figure 1

Part 11 Remediation Analysis Questions *(Continued)*

46.	Does test evidence exist to demonstrate operational checks are performed?
47.	Are there checks in place to ensure that only authorized persons may use the system?
48.	Can only authorized persons electronically sign a record?
49.	Can only authorized persons access the electronic records?
50.	Does the system check authority levels before allowing a record to be signed electronically? (Can unauthorized persons alter an electronic record?)
51.	Can only authorized persons perform operations?
52.	Are there procedures in place for granting, maintaining, and/or removing privileges?
53.	Does a time out feature exist?
54.	Does test evidence exist to demonstrate authority checks are performed?
55.	Does the system check the validity of the source of any data or operational instruction?
56.	Are records traceable to the creation source?
57.	Does test evidence exist to demonstrate device checks are performed?
58.	Are training records for developers available?
59.	Are training records for support and maintenance personnel available?
60.	Do training records for users exist?
61.	Does a procedure exist on documentation training?
62.	Does a procedure exist defining the use of electronic signatures?
63.	Does user acknowledgement of the equivalence of handwritten and electronic signatures exist?
64.	Does the procedure include the process of delegating electronic signature authority?
65.	Does the vendor have an acceptable document management process?
66.	Does information technologies have an acceptable document management process?
67.	Does the system owner have an acceptable document management process?
68.	Is this system considered an open system? If yes, answer questions 69 and 70. If no, questions 69 and 70 are not applicable.
69.	Does the system use document encryption?
70.	Does the system utilize digital signatures?
71.	Does the signed electronic record contain the printed name of the signer?
72.	Does the signed electronic record contain the date and time the electronic signature was executed?
73.	Does the signed electronic record contain the meaning of the electronic signature?
74.	Is the manifestation of the electronic signature under the same controls as electronic records?
75.	Is the electronic signature included in all human readable forms of the record?
76.	Does test evidence exist documenting signature manifestation?
77.	Are electronic signatures and handwritten signatures executed to electronic records linked to their respective electronic record?
78.	Can the electronic signature be *excised* by ordinary means?
79.	Can the electronic signature be *copied* by ordinary means?
80.	Can the electronic signature be *transferred* by ordinary means?
81.	If the electronic record is changed, is the link between the signature and electronic record broken? (handwritten or electronic signature)
82.	Does test evidence exist demonstrating the link between the signature and electronic record? (handwritten signature or electronic signature)
83.	Is the electronic signature unique to one individual?
84.	Can electronic signatures be reused or reassigned to other individuals?
85.	Does the system check for duplicate electronic signatures?
86.	Does test evidence exist to demonstrate the uniqueness of electronic signatures?

(Continued)

Figure 1

Part 11 Remediation Analysis Questions *(Continued)*

87.	Is there evidence that the identity of an individual is verified prior to assigning an electronic signature?
88.	Are there procedures in place to verify and document the identity of individuals prior to assigning an electronic signature?
89.	Has a certification letter been issued, notifying the agency that electronic signatures in the system are intended to be the legally binding equivalent of traditional handwritten signatures?
90.	Has additional testimony been provided concerning the attributability of electronic signatures?
91.	Has electronic signature training been performed and documented?
92.	Is periodic training on electronic signatures performed?
93.	Does a procedure exist documenting that an electronic signature is the legal equivalent of a handwritten signature?
94.	Does the non-biometric signature require at least two distinct components?
95.	Does the first signing during one controlled access session require both components of the electronic signature to be entered?
96.	Do subsequent signings within a single session include at least the “secret” component?
97.	When an individual executes one or more signings, not performed during a single continuous period of controlled access, is each signing executed, using both components of the electronic signature?
98.	Can non-biometric electronic signatures be used by an individual other than their genuine owner?
99.	Are non-biometric signatures administered, so that collaboration of two or more individuals is required for falsification?
100.	Are passwords stored encrypted, and therefore unavailable for viewing?
101.	Does the requirements document include a definition of “Continuous periods of use”?
102.	Does the requirements document define how the system handles a non-continuous session?
103.	Can biometric electronic signatures be used by individuals, other than their genuine owners?
104.	Is test evidence available for biometric electronic signatures?
105.	Can biometric files (i.e., images) be copied?
106.	Is user ID and password uniqueness maintained?
107.	Does the system employ checks for duplication of user IDs?
108.	Are user ID and password issuances periodically recalled, checked, or revised?
109.	Does a procedure exist surrounding user ID and password management?
110.	Are user ID and password management built into the system?
111.	Is there a loss management process for lost, stolen, or otherwise compromised devices?
112.	Is there a management process for issuing replacement devices?
113.	Are there transaction safeguards to prevent unauthorized use of passwords or identification codes?
114.	Does the system detect and report attempted unauthorized use?
115.	Are transaction safeguards defined in the requirements?
116.	Does test evidence exist for transaction safeguards?
117.	Does a procedure exist to define how to monitor alerts?
118.	Are devices tested to ensure that they work?
119.	Does test evidence exist to insure devices have not been altered?
120.	Does test evidence exist for device testing?
121.	Does a procedure exist for periodic device testing?

Remediation does dovetail into current GxP (Good Manufacturing Practice [GMP], Good Laboratory Practice [GLP], Good Clinical Practice [GCP]), and validation activities. The withdrawal of the old guidance documents did raise concerns, however, the new one does provide clarity with regard to legacy systems. The document control aspect of Part 11 compliance ensures audit trails and retrieval of archived data, and provides fodder for new engagements in research. The experiments of yesterday now can be the valued investment for future discovery. ❑

Figure 2

Part 11 Remediation Analysis

Number	21 CFR Part 11 Requirements	Gap Analysis/ Finding	Gap Procedural/ Technical	Remediation Approach
Validation 11.10 (a)				
1	Does a requirement specification exist?	Requirements specification does not exist.	P	Create a requirements specification per the System Lifecycle (SLC) process.
2	Does a design document exist?	Design document	P	No action required. An audit was conducted in January, 2002. The status of this firm is regarded as *Fully Approved*.
3	Does testing documentation exist?	Limited testing documentation exists for this system.	P	A gap analysis on the vendor-supplied validation package will be performed. Gaps in the existing vendor validation package will be tested and recorded in the appropriate validation documentation.
4	Does an operating procedure exist?	Operating procedure does not exist.	P	An EOP for this system does not exist and needs to be created and implemented.
5	Does a system development lifecycle exist?	System development lifecycle exists.	P	The SLC process exists, and will be applied to this system.
6	Does a validation plan exist?	Validation plan does not exist.	P	A validation plan following the SLC guidelines will be developed to address identified gaps.
7	Does a validation report exist?	Validation report does not exist.	P	A validation report following the SLC guidelines will be written upon completion of the validation.
8	Does training documentation exist?	Training documentation exists.	P	No action required. A *Training program* exists and is effective.
9	Does a change control procedure exist?	Change control procedure exists.	P	No action required. *Equipment change control* exists and is effective.
10	Is there evidence that data conversion exists?	Evidence of data conversion does not exist.	T	Data conversion will be tested and recorded in the appropriate validation documentation.
11	Does a support plan exist?	Support plan does not exist.	P	Refer to remediation approach #4.

(Continued)

Figure 2

Part 11 Remediation Analysis *(Continued)*

Number	21 CFR Part 11 Requirements	Gap Analysis/ Finding	Gap Procedural/ Technical	Remediation Approach
				The support plan (maintenance agreement) will be identified when a system specific Standard Operating Procedure (SOP) is created and implemented.
12	Has a vendor audit been performed?	Vendor Audit has been performed.	P	No action required. An audit of Agilent was conducted in January, 2002. The status of this firm is regarded as fully approved.
Record Availability 11.10(b)				
13	Are all records available for viewing?	All records are not available for viewing.	T	Implement the built-in security features in the application software, and Windows® operating system. Upon implementation, records will be secure and available for viewing.
14	Are all records available for copying?	All records are not available for copying.	T	See remediation approach #13. Upon implementation, all records will be available for copying.
15	Are all records available for inspection?	All records are not available for inspection.	T	See remediation approach #13. Upon implementation, all records will be available for inspection.
16	Does a procedure for providing records exist?	A procedure for providing records exists.	P	No action required. A *procedure* exists and is effective.
17	Does test evidence exist to demonstrate record availability?	Test evidence does not exist to demonstrate record availability.	P	Functional requirements for record availability will be tested and recorded in the appropriate validation documentation.
Record Retention 11.10(c)				
18	Can records be deleted?	Records can be deleted.	T	Implement the built-in security features in the application software, and Windows operating system. Upon implementation, records will not be able to be deleted.
19	Are records proven to be accurate?	Records cannot be proven to be accurate.	T	See remediation approach #18.

(Continued)

Figure 2

Part 11 Remediation Analysis *(Continued)*

Number	21 CFR Part 11 Requirements	Gap Analysis/ Finding	Gap Procedural/ Technical	Remediation Approach
				Upon implementation, all records can be proven to be accurate.
20	Are records retrievable?	Records are not retrievable.	T	See remediation approach #18. Upon implementation, all records will be retrievable.
21	Has a capacity analysis been performed?	A capacity analysis has not been performed.	P	A capacity analysis will be performed and recorded in the appropriate validation documentation.
22	Does an electronic records retention policy exist?	An electronic records retention policy exists.	P	No action required. Policy exists and is effective.
23	Does backup/restore procedures exist?	A backup/restore procedure exists.	P	Backup and recovery procedure exists. Restore procedure does not exist. Place the system on a server that is backed up, and ensure that all records, including audit trail and security, are backed up. Develop a backup/restore procedure for the system, and add a server, perhaps with the application.
24	Do archive/recovery procedures exist?	Archive/recovery procedures do not exist. Recovery procedure exists. See remediation approach #23.	P	Data archive/recovery are a shared responsibility. Assist in developing and implementing an appropriate archive and recovery procedure.
25	Does a disaster recovery procedure exist?	A disaster recovery procedure exists.	P	Disaster recovery procedure does not cover this system. A continuity plan exists and is effective. It covers all laboratories.
26	Is virus protection installed on the Personal Computer (PC)?	Virus protection is not installed on the PC.	T	Verify virus protection exists on the PC. If not, install corporate approved virus protection.
27	Is virus protection installed on the server? (if applicable)	Virus protection is not installed on the server.	T	Verify virus protection exists on the server. If not, install corporate approved virus protection.
				(Continued)

Figure 2

Part 11 Remediation Analysis *(Continued)*

Number	21 CFR Part 11 Requirements	Gap Analysis/ Finding	Gap Procedural/ Technical	Remediation Approach
28	Does test evidence exist to demonstrate accurate and timely retrieval of records?	Test evidence does not exist to demonstrate accurate and timely retrieval of records.	P	Functional requirements for accurate and timely retrieval of records will be tested and recorded in the appropriate validation documentation.
Limited Access 11.10(d)				
29	Do controls limiting system access exist?	There are no controls limiting system access.	T	Implement the built-in security features in the application software, and Windows operating system. Set up the controls limiting system access. Upon implementation, there will be controls limiting system access.
30	Does a historical users list exist?	A historical list of users is not available.	P	A historical list of users is not available through the software. The administrator can scroll through the users and verify rights, but a historical list is not available. Develop and implement a procedure outlining how a historical user list will be controlled. This could be included in the system administrator SOP.
31	Does an account management procedure exist?	An account management procedure does not exist.	P	Develop and implement a procedure outlining how account management on the application software and operating software will be controlled. This could be included in the system administrator SOP.
32	Does test evidence exist to demonstrate system access is limited?	Test evidence does not exist to demonstrate system access is limited.	P	Functional requirements for demonstrating system access is limited, and will be tested and recorded in the appropriate validation documentation.
Audit Trail 11.10(e)				
33	Does a secure, non-editable audit trail exist?	A secure, non-editable audit trail does not currently exist.	T	Implement the secure non-editable audit trail functionality within the application software.
				(Continued)

Figure 2

Part 11 Remediation Analysis *(Continued)*

Number	21 CFR Part 11 Requirements	Gap Analysis/ Finding	Gap Procedural/ Technical	Remediation Approach
34	Is there a computer-generated audit trail?	A computer generated audit trail is not available.	T	Refer to remediation approach #33. Upon implementation, a computer-generated audit trail is available.
35	Is there a secure, computer-generated time stamped audit trail that independently records the date and time?	A secure date/time stamp is not included in the audit trail.	T	Refer to remediation approach #33. Upon implementation, there is a date/time stamp included in the audit trail.
36	Does the audit trail document the operator's entries and actions that create, modify, or delete electronic records?	The audit trail does not document operator entries and actions that create, modify, or delete electronic records.	T	Refer to remediation approach #33. Upon implementation, the audit trail is complete. It records all events that are created, modified, and/or deleted.
37	Does the audit trail retain previous values, and are those previous values available for viewing?	The audit trail does not retain previous values, therefore, previous values are not available for viewing.	T	Refer to remediation approach #33. Upon implementation, the audit trail is complete, and keeps track of actions performed, with the data, even if the result of the operation was rejected.
38	Is the audit trail retained as long as the electronic record?	The audit trail is not retained as long as the electronic record.	T	Refer to remediation approach #33. Upon implementation, the audit trail is stored in the "history" data block, and is retained as long as the electronic record.
39	Is the audit trail available for review and copying at the request of the FDA?	The audit trail is not available for FDA review.	T	Refer to remediation approach #33. Upon implementation, the audit trail is available for agency review. The audit trail will be made available for review and copying at the request of the FDA.
40	Are the system administrator functions included in the audit trail?	System administrator functions are not included in the audit trail.	T	Refer to remediation approach #33. System administrator functions are not included in the audit trail. This could be included in the system administrator SOP.

(Continued)

Figure 2

Part 11 Remediation Analysis *(Continued)*

Number	21 CFR Part 11 Requirements	Gap Analysis/ Finding	Gap Procedural/ Technical	Remediation Approach
41	Is the time source obtained from a secure location?	The time source is not obtained from a secure location.	T	Refer to remediation approach #33. Upon implementation, the time source is obtained from a secure location. The time stamp will be taken from the Windows operating system. The users will not have access to change the time or date on the system.
42	Are controls in place to manage the Data Base Administrator's (DBA) responsibilities?	Controls are not in place that manage the DBA's responsibilities.	P	Develop and implement a system administrator SOP to include management of the system administrator's responsibilities.
43	Does test evidence exist to demonstrate the functionality of the audit trail?	Test evidence does not exist to demonstrate the functionality of the audit trail.	P	Functional requirements of the audit trail will be tested and recorded in the appropriate validation documentation.
Operational System Checks 11.10(f)				
44	Are sequences built in and enforced?	Sequences are not used on this system, therefore, they are not required to be enforced.	N/A	Not applicable.
45	Are sequences documented?	Sequences are not used on this system, therefore, documentation of sequences do not exist.	N/A	Not applicable.
46	Does test evidence exist to demonstrate operational checks are performed?	Operational checks are not performed on this system, therefore, test evidence is not required.	N/A	Not applicable.
Authority Checks 11.10(g)				
47	Are there checks in place to ensure that only authorized persons may use the system?	There are no checks in place to ensure that only authorized persons may use the system.	T	Implement the security features of the application software, and Windows operating system. Upon implementation, checks will be in place to ensure that only authorized persons may use the system.

(Continued)

Figure 2

Part 11 Remediation Analysis *(Continued)*

Number	21 CFR Part 11 Requirements	Gap Analysis/ Finding	Gap Procedural/ Technical	Remediation Approach
48	Can only authorized persons electronically sign a record?	The system has electronic signature functionality, but it has not been implemented.	T	Implement the electronic signature functionality of the application software. Upon implementation, the system ensures that only users registered in a separate signature database can electronically sign a document.
49	Can only authorized persons access the electronic records?	There are no checks in place to ensure that only authorized persons can access electronic records.	T	Refer to remediation approach #47. Upon implementation, checks will be in place to ensure that only authorized persons can access electronic records.
50	Does the system check authority levels before allowing a record to be signed electronically? (Can unauthorized persons alter an electronic record?)	There are no checks in place to ensure that only authorized persons can alter an electronic record.	T	Refer to remediation approach #48. Upon implementation, assign electronic signature rights to appropriate persons, and use the security feature to ensure only authorized persons can sign a record.
51	Can only authorized persons perform operations?	There are no checks in place to ensure that only authorized persons can perform operations.	T	Implement the security features of the application software, and configure the user rights settings to limit access to authorized persons.
52	Are there procedures in place for granting, maintaining, and/or removing privileges?	There are no procedures in place for granting, maintaining, and removing privileges.	P	Develop and implement a system administrator SOP to include definition of system administrator duties and responsibilities.
53	Does a time out feature exist?	A time out feature exists, but is not in use for all systems.	T	Implement the time out feature available. Configure the time out feature to comply with corporate and site policies and procedures.
54	Does test evidence exist to demonstrate authority checks are performed?	Test evidence does not exist to demonstrate authority checks are performed.	P	Functional requirements for authority checks will be tested and recorded in the appropriate validation documentation.

(Continued)

Figure 2

Part 11 Remediation Analysis *(Continued)*

Number	21 CFR Part 11 Requirements	Gap Analysis/ Finding	Gap Procedural/ Technical	Remediation Approach
Device Checks 11.10(h)				
55	Does the system check the validity of the source of any data or operational instruction?	The system does not check the validity of the source of the data or operational instruction.	T	Implement the application software. Upon implementation, the software has the functionality to perform device checks, and verify the validity of the data, and/or operational instruction.
56	Are records traceable to the creation source?	Records are not traceable to the creation source.	T	Refer to remediation approach #55. Upon implementation, records will be traceable to the creation source.
57	Does test evidence exist to demonstrate device checks are performed?	Test evidence does not exist to demonstrate device checks are performed.	P	Functional requirements for device checks will be tested and recorded in the appropriate validation documentation.
Training 11.10(i)				
58	Are training records for developers available?	Training records for developers are available.	P	No action required. An audit was conducted in January, 2002. The status of this firm is regarded as *fully approved.*
59	Are training records for support and maintenance personnel available?	Training records for support and maintenance personnel are available.	P	No action required. A *Training program* exists and is effective.
60	Do training records for users exist?	Training records for users exist.	P	No action required. *Training program* exists and is effective.
61	Does a procedure exist on documentation training?	A procedure for documentation training exists.	P	No action required. *Training program*, exists and is effective.
Electronic Signature Procedure 11.10(j)				
62	Does a procedure exist defining the use of electronic signatures?	A procedure exists for the use of electronic signatures.	P	No action required. SOP on *Compliance with 21 CFR Part 11: Electronic Signatures* exists and is effective.
63	Does user acknowledgement of the equivalence of handwritten and electronic signatures exist?	User acknowledgement of the equivalence of handwritten and electronic signatures exists.	P	No action required. SOP on *compliance with 21 CFR Part 11: Electronic Signatures* requires users of 21 CFR Part 11 applicable systems to acknowledge this in writing by utilizing form. *(Continued)*

Figure 2

Part 11 Remediation Analysis *(Continued)*

Number	21 CFR Part 11 Requirements	Gap Analysis/ Finding	Gap Procedural/ Technical	Remediation Approach
				Signed forms are retained in the individual's training file.
64	Does the procedure include the process of delegating electronic signature authority?	The procedure includes the process of delegating electronic signature authority.	P	No action required. *SOP on compliance with 21 CFR Part 11: Electronic Signatures* states that delegation rights will be facilitated within the context of the system and/or application.
Document Control 11.10(k)				
65	Does the vendor have an acceptable document management process?	The vendor has an acceptable document management process	P	No action required. An audit of Agilent was conducted in January, 2002. The status of this firm is regarded as *fully approved*.
66	Does information technologies have an acceptable document management process?	An acceptable document management process exists.	P	No action required. An acceptable document management process exists. Numerous SOPs exist, and are approved to support this process.
67	Does the system owner have an acceptable document management process?	The sytem owner does not have a document management process. The QAC group manages all documentation.	P	No action required. *Standard operating procedures*. There is change control and a GMP documentation group.
Open Systems 11.30				
68	Is this system considered an open system? If yes, answer questions 69 and 70. If no, questions 69 and 70 are not applicable.	No. This is a closed system and controls for open systems do not apply.	N/A	Not applicable.
69	Does the system use document encryption?	This is a closed system and controls for open systems do not apply.	N/A	Not applicable.
70	Does the system utilize digital signatures?	This is a closed system and controls for open systems do not apply.	N/A	Not applicable.
Signature Manifestation 11.50				
71	Does the signed electronic record contain the printed name of the signer?	Currently, signatures are handwritten.	T	Implement the electronic signature functionality within the application software.

(Continued)

Figure 2

Part 11 Remediation Analysis *(Continued)*

Number	21 CFR Part 11 Requirements	Gap Analysis/ Finding	Gap Procedural/ Technical	Remediation Approach
				Upon implementation, the "Name" entry of an electronic signature requires first and last name.
72	Does the signed electronic record contain the date and time the electronic signature was executed?	Currently signatures are handwritten.	T	Refer to remediation approach #71, if applicable… Upon implementation, date and time are automatically added to the signature entry in the data file, and are documented in the audit trail, as well.
73	Does the signed electronic record contain the meaning of the electronic signature?	Currently, signatures are handwritten.	T	Refer to remediation approach #71.
74	Is the manifestation of the electronic signature under the same controls as electronic records?	Currently, signatures are handwritten.	T	Refer to remediation approach #71.
75	Is the electronic signature included in all human readable forms of the record?	Currently, signatures are handwritten.	T	Refer to remediation approach #71.
76	Does test evidence exist documenting signature manifestation?	Test evidence does not exist to demonstrate signature manifestation.	P	Functional requirements to demonstrate the signature manifestation will be tested and recorded in the appropriate validation documentation.
Record/Signature Linking 11.70				
77	Are electronic signatures and handwritten signatures executed to electronic records linked to their respective electronic record?	There is no link between the handwritten signature and the electronic record.	T	Implement the electronic signature functionality within the application software. Upon implementation, linking between the electronic signature and the electronic record exists.
78	Can the electronic signature be *excised* by ordinary means?	Currently, a handwritten signature is executed to an electronic record.	T	Refer to remediation approach #77. Upon implementation, electronic signatures cannot be excised by ordinary means.
79	Can the electronic signature be *copied* by ordinary means?	Currently, signatures are handwritten.	T	Refer to remediation approach #77. Upon implementation, electronic signatures cannot be copied by ordinary means.

(Continued)

Figure 2

Part 11 Remediation Analysis *(Continued)*

Number	21 CFR Part 11 Requirements	Gap Analysis/ Finding	Gap Procedural/ Technical	Remediation Approach
80	Can the electronic signature be *transferred* by ordinary means?	Currently, signatures are handwritten.	T	Refer to remediation approach #77. Upon implementation, electronic signature cannot be transferred by ordinary means.
81	If the electronic record is changed, is the link between the signature and electronic record broken? (handwritten or electronic signature)	Currently, signatures are handwritten. If the record changes, the link between the handwritten signature and electronic record is broken.	T	Refer to remediation approach #77. Upon implementation, if the electronic record is changed, the link between the signature and original electronic record is not broken.
82	Does test evidence exist demonstrating the link between the signature and electronic record? (handwritten or electronic signature)	Test evidence does not exist demonstrating the link between the signature and electronic re-record? (handwritten or electronic signature)	P	Functional requirements linking the electronic signature and the electronic record will be tested and recorded in the appropriate validation documentation.
Electronic Signature Uniqueness 11.100(a)				
83	Is the electronic signature unique to one individual?	Currently, signatures are handwritten.	T/P	Implement the electronic signature functionality within the application software. Upon implementation, the electronic signature will be unique to each individual. Develop a system administrator SOP, and include how to distinguish between two individuals with the same name
84	Can electronic signatures be reused or reassigned to other individuals?	Currently, signatures are handwritten.	T	Refer to remediation approach #83. Upon implementation, electronic signatures cannot be reused or reassigned to other individuals.
85	Does the system check for duplicate electronic signatures?	Currently, signatures are handwritten.	T	Refer to remediation approach #83. Upon implementation, the system disallows duplicate electronic signatures.
86	Does test evidence exist to demonstrate the uniqueness of electronic signatures?	Currently, signatures are handwritten.	P	Functional requirements for the uniqueness of electronic signatures will be tested and recorded in the appropriate validation documentation.

(Continued)

Figure 2

Part 11 Remediation Analysis *(Continued)*

Number	21 CFR Part 11 Requirements	Gap Analysis/ Finding	Gap Procedural/ Technical	Remediation Approach
Identity Verification 11.100(b)				
87	Is there evidence that the identity of an individual is verified prior to assigning an electronic signature?	There is no evidence that the identity of an individual is verified prior to assigning an electronic signature.	P	Develop and implement a procedure for verifying and documenting an individual's identity, prior to assigning an electronic signature. This can be incorporated into the system administrator SOP.
88	Are there procedures in place to verify and document the identity of individuals prior to assigning an electronic signature?	There are no procedures in place to verify and document the identity of individuals prior to assigning an electronic signature.	P	Refer to remediation approach #87.
Attributability 11.100(c)				
89	Has a certification letter been issued, notifying the agency that electronic signatures in the system are intended to be the legally binding equivalent of traditional handwritten signatures?	A certification letter has been issued notifying the agency that electronic signatures in the system are intended to be the legally binding equivalent of traditional handwritten signatures.	P	No action required. A certification letter was sent to the FDA and dated August 20, 1997. A copy of this letter is is available on the intranet home page.
90	Has additional testimony been provided concerning the attributability of electronic signatures?	Additional testimony has been provided concerning the attributability of electronic signatures.	P	No action required. SOP on *Compliance with 21 CFR Part 11: Electronic Signatures* exists and is effective. This SOP states that the electronic signature is the legal equivalent of a handwritten signature. All staff has signed the certification form.
91	Has electronic signature training been performed and documented?	Training on electronic signatures has been performed and documented.	P	No action required. An SOP on *Compliance with 21 CFR Part 11: Electronic Signatures* was made effective on June 3, 2002. Staff has been trained on this SOP. Training is documented per training program. Orientation is required per SOP for all colleagues, including all temporary staff.

(Continued)

Figure 2

Part 11 Remediation Analysis *(Continued)*

Number	21 CFR Part 11 Requirements	Gap Analysis/ Finding	Gap Procedural/ Technical	Remediation Approach
				Orientation includes an introduction to 21 CFR Part 11.
92	Is periodic training on electronic signatures performed?	Periodic training on electronic signatures is performed.	P	*Training program* exists and is effective. 21 CFR Part 11 is included in GMP orientation training, but needs to be incorporated into periodic review training.
93	Does a procedure exist documenting that an electronic signature is the legal equivalent of a handwritten signature?	A procedure exists documenting that an electronic signature is the legal equivalent of a handwritten signature.	P	No action required. SOP on *Compliance with 21 CFR Part 11: Electronic Signatures* exists and is effective.
Non-Biometric Electronic Signature Controls 11.200(a)				
94	Does the non-biometric signature require at least two distinct components?	Currently, signatures are handwritten.	T	Implement the electronic signature functionality within the application software. Upon implementation, the non-biometric electronic signature will require two distinct components.
95	Does the first signing during one controlled access session require both components of the electronic signature to be entered.	Currently, signatures are handwritten.	T	Refer to remediation approach #94. Upon implementation, the first signing during one controlled access session requires both components of the signature to be entered.
96	Do subsequent signings within a single session include at least the “secret” component?	Currently, signatures are handwritten.	T	Refer to remediation approach #94. Upon implementation, subsequent signings within a single session include at least the “secret” component.
97	When an individual executes one or more signings, not performed during a single continuous period of controlled access, is each signing executed, using both components of the electronic signature?	Currently, signatures are handwritten.	T	Refer to remediation approach #94. Upon implementation, when an individual executes one or more signings, not performed during a single continuous period of controlled access, each signing is executed, using both components of the electronic signature.

(Continued)

Figure 2

Part 11 Remediation Analysis *(Continued)*

98	Can non-biometric electronic signatures be used by an individual other than their genuine owner?	Currently, signatures are handwritten.	T	Refer to Remediation Approach #94. Upon implementation, non-biometric electronic signatures can only be used by their genuine owner.
99	Are non-biometric signatures administered, so that collaboration of two or more individuals is required for falsification?	Currently, signatures are handwritten.	T	Refer to Remediation Approach #94. Upon implementation, non-biometric signatures are administered, so that collaboration of two or more individuals is required for falsification.
100	Are passwords stored encrypted and therefore unavailable for viewing?	Currently, signatures are handwritten.	T	Refer to Remediation Approach #94. Upon implementation, passwords are stored encrypted, and are therefore unavailable for viewing.
101	Does the requirements document include a definition of "Continuous periods of use"?	Currently, signatures are handwritten.	P	The requirements document will be written to include a "Continuous period of use" definition.
102	Does the requirements document define how the system handles a non-continuous session?	Currently, signatures are handwritten.	P	The requirements document will define how the system handles a non-continuous period of use.
Biometric Signature Controls 11.200(b)				
103	Can biometric electronic signatures be used by individuals, other than their genuine owners?	Not applicable. Biometric signatures are not utilized by this system.	N/A	No action required.
104	Is test evidence available for biometric electronic signatures?	Not applicable. Biometric signatures are not utilized by this system.	N/A	No action required.
105	Can biometric files (i.e., images) be copied?	Not applicable. Biometric signatures are not utilized by this system.	N/A	No action required.
ID/Password Uniqueness 11.300(a)				
106	Is user ID and password uniqueness maintained?	User ID and password uniqueness is maintained within the application software and the operating system software.	T	Verify if the software does this, or if this is only when the software is set up to do so. If so, this will be included in the system administrator SOP.

(Continued)

Figure 2

Part 11 Remediation Analysis *(Continued)*

Number	21 CFR Part 11 Requirements	Gap Analysis/ Finding	Gap Procedural/ Technical	Remediation Approach
107	Does the system employ checks for duplication of user IDs?	The system employs checks for duplication of user IDs.	T	The application software does not allow duplicate user IDs in the system.
ID/Password Uniqueness 11.300(b)				
108	Are user ID and password issuances periodically recalled, checked, or revised?	User ID and password issuances are not periodically recalled, checked, or revised.	P	Develop and implement a procedure surrounding user ID and password issuances. This should include periodically recalling, checking, or revising. This could be included in the system administrator SOP.
109	Does a procedure exist surrounding user ID and password management?	A procedure does not exist surrounding user ID and password management.	P	Develop and implement a procedure surrounding user ID and password management. This could be included in the system administrator SOP.
110	Are user ID and password management built into the system?	User ID and password management are built into the system, but the functionality has not been implemented.	T	Implement the user ID and password management feature built into the application software.
Device Management 11.300(c)				
111	Is there a loss management process for lost, stolen, or otherwise compromised devices?	Not applicable. Identification devices are not utilized by this system.	N/A	No action required.
112	Is there a management process for issuing replacement devices?	Not applicable. Identification devices are not utilized by this system.	N/A	No action required.
Transaction Safeguards 11.300(d)				
113	Are there transaction safeguards to prevent unauthorized use of passwords or identification codes?	Transaction safeguards to prevent unauthorized use of passwords or identification codes do not exist.	T	Implement the security functionality within the application software. Upon implementation, transaction safeguards to prevent unauthorized use of passwords or identification codes exist.
114	Does the system detect and report attempted unauthorized use?	The system does not detect and report attempted unauthorized user.	T	Refer to Remediation Approach #113
115	Are transaction safeguards defined in the requirements?	Transaction safeguards are not defined in the requirements documentation.	P	The transaction safeguards will be defined in the requirements documentation.

(Continued)

Figure 2

Part 11 Remediation Analysis *(Continued)*

Number	21 CFR Part 11 Requirements	Gap Analysis/ Finding	Gap Procedural/ Technical	Remediation Approach
116	Does test evidence exist for transaction safeguards?	Test evidence does not exist for transaction safeguards.	P	Functional requirements for the transaction safeguards will be tested and recorded in the appropriate validation documentation.
117	Does a procedure exist to define how to monitor alerts?	A procedure defining how to monitor alerts is not in place.	P	Develop and implement a procedure that defines how to monitor alerts. This could be included in the system administrator SOP.
Electronic Signature Device Tests 11.300(e)				
118	Are devices tested to ensure that they work?	Not applicable. Identification devices are not utilized by this system.	N/A	No action required.
119	Does test evidence exist to insure devices have not been altered?	Not applicable. Identification devices are not utilized by this system.	N/A	No action required.
120	Does test evidence exist for device testing?	Not applicable. Identification devices are not utilized by this system.	N/A	No action required.
121	Does a procedure exist for periodic device testing?	Not applicable. Identification devices are not utilized by this system.	N/A	No action required.

About the Author

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Suggested Reading

- FDA. "Code of Federal Regulations, Title 21 Food and Drugs, Part 11 Electronic Records; Electronic Signatures: Final Rule." *Federal Register*. Vol., 62 No. 54. March 20, 1997. Pp. 13429-13466.
- FDA. "Draft Guidance for Industry on "Part 11, Electronic Records, Electronic Signatures-Scope and Application;' Availability of Draft Guidance and Withdrawal of Draft Part 11 Guidance Documents and a Compliance Policy Guide." *Federal Register*. Vol. 68, No. 37. February 25, 2003.Pp. 8775-8776.
- L. Huber and W. Winter. "Part 11 Is Not Going Away, The New Electronic Records Draft Guidance." *BioPharm International*. May 2003. Pp. 28-34.

Figure 3 is presented on the following pages

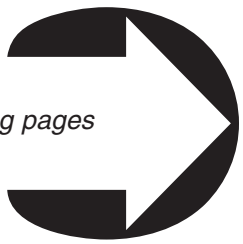

Figure 3

Quality Task Matrix

Process Step	Deliverables
Planning and Analysis Phase	
Purchasing activities	Category determination
	Risk assessment
	Justification/business needs assessment
	Review existing documentation
	Vendor assessment questionnaire (20 questions)
	Vendor demo
	Part 11 scope assessment (four questions)
	Review of assessment package
	Vendor audit
	Vendor audit report
	Support group notification and development of integration requirements e.g., safety, facilities, Information Technology (IT)
	Review of assessment package/approval for purchase
	Purchase system
	Quality Assurance (QA) notification of purchase
	Quality Assurance (QA) adds inventory item
Receiving activities	Receive system in-house
Validation plan	System Lifecycle (SLC) quality and task matrix
	Validation plan
Requirements/specifications	Requirements/specifications
	Requirements/specifications traceability matrix
Critical points of failure analysis	Critical points of failure analysis
Validation package review	Validation documentation set (Vendor or internal-supplied packet) and gap analysis of validation documentation set, as supplied from vendor or internal group.
Internal IT activities/planning – also can include other support groups	IT templates as required – other support group processes as required
Quality Assurance (QA) review	Review or closure of planned deviations
	Approval of deliverables
Quality Development and Testing Phase	
Testing and quality document planning/development	Development of test plan (Installation Qualification/ Operation Qualification/Performance Qualification [IQ/OQ/PQ])
	Development of test scripts (address gaps as required)
	Draft procedures
	Draft user guides
	Update requirements/specifications/traceability matrix
Internal IT testing activities – also can include other support groups	IT process steps as required (development, network connectivity, etc.) – other support group processes, as required
Quality Assurance (QA) review	Review or closure of planned deviations
	Approval of deliverables

(Continued)

Figure 3

Quality Task Matrix *(Continued)*

Process Step	Deliverables
Acceptance Testing Phase	
Acceptance test training	Training of testers
Hardware – Installation Qualification (IQ)	Document IQ testing
	Approval of IQ documentation
Software – Installation Qualification (IQ)	Document IQ testing
	Approval of IQ documentation
Hardware – Operational Qualification (OQ)	Document OQ testing
	Approval of OQ documentation
Software – Operational Qualification (OQ)	Document OQ testing
	Approval of OQ documentation
Hardware – Performance Qualification (PQ)	Document PQ testing
	Approval of PQ documentation
Software – Performance Qualification (PQ)	Document PQ testing
	Approval of PQ documentation
	Update requirements/specifications/traceability matrix
Quality Assurance (QA) review	Review or closure of planned deviations
	Approval of deliverables
Validation report	Validation report
	Approval of validation report
Implementation and Maintenance Phase	
Rollout activities	Approve procedures
	Approve user guides
	User training
	Matrix completed and system released for use

Article Acronym Listing

ALCN:	Analytical Laboratory Computer Networking
DBA:	Data Base Administrator
FDA:	Food and Drug Administration
GxP:	Good Manufacturing Practice (GMP), Good Laboratory Practice (GLP), Good Clinical Practice (GCP)
IQ:	Installation Qualification
IT:	Information Technology
OQ:	Operational Qualification
PC:	Personal Computer
PQ:	Performance Qualification
QA:	Quality Assurance
SLC:	System Lifecycle
SOP:	Standard Operating Procedure

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What Companies Should Know And Consider When Designing A CAPA System PART I

By ***Gabriela Bodea***

INTRODUCTION

Corrective and Preventive Action (CAPA), as a subsystem, integrates all quality subsystems, thereby closing a "quality loop." CAPA represents one of the mechanisms that ensures continuous improvement within an organization; along with customer satisfaction measurements, internal audits, trend recording, and non-conforming product control. Once the targeted performance is reached, new performance criteria are set to realize continuous improvement and ever more focused quality. In this way, CAPA actualizes the philosophy of the spiral helix depicted by the International Organization for Standardization (ISO) 9001: 2000.

A CAPA program is established to serve as an uninterrupted element for the improvement of product, process, and quality systems. Think of it as a quality improvement vehicle that operates as a two-loop system – a reactive loop and a proactive loop. With the Food and Drug Administration's (FDA) new systemic audit inspection approach and its emphasis on risk-based management, utilizing a CAPA program must be proactive. The following points are business baseline requirements for any CAPA system.

WHY IMPLEMENT A CAPA SYSTEM?

Implementing an effective, smoothly functioning corrective and preventive action system is important because CAPA:

- Is a regulatory requirement of the U.S. FDA Quality System (QS) regulation.
- Is a requirement of ISO 9001: 2000 and ISO 17025.
- Represents a quality improvement tool.

To avoid non-conformities in regulated areas and their repercussions, but more importantly to ensure product safety and consistency, companies should embrace a CAPA system. This will ensure customer satisfaction by correcting existing problems or by implementing controls to prevent potential problems from occurring, both of which are key for continuous customer satisfaction. Ultimately, establishing and implementing a well thought out CAPA system represents good business practice.

Regulatory Requirements

CAPA is an area of interest for both the FDA and ISO 9000 and for everyone concerned with quality. CAPA is not restricted to QS regulations or to the Quality System Inspection Technique (QSIT) Guide. The ability to correct existing problems and to implement controls to prevent potential problems from occurring is essential for sustained customer

satisfaction and effective business practice.

➤ *CFR 820, Subpart J*

Corrective and Preventive Action, § 820.100,[1] states:

(a) Each manufacturer shall establish and maintain procedures for implementing corrective and preventive action. The procedures shall include requirements for:
  (1) Analyzing processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned product, and other sources of quality data to identify existing and potential causes of nonconforming product, or other quality problems. Appropriate statistical methodology shall be employed where necessary to detect recurring quality problems;
  (2) Investigating the cause of nonconformities relating to product, processes, and the quality system;
  (3) Identifying the action(s) needed to correct and prevent recurrence of nonconforming product and other quality problems;
  (4) Verifying or validating the corrective and preventive action to ensure that such action is effective and does not adversely affect the finished device;
  (5) Implementing and recording changes in methods and procedures needed to correct and prevent identified quality problems;
  (6) Ensuring that information related to quality problems or nonconforming product is disseminated to those directly responsible for assuring the quality of such product or the prevention of such problems; and
  (7) Submitting relevant information on identified quality problems, as well as corrective and preventive actions, for management review.

(b) All activities required under this section, and their results, shall be documented.

➤ *FDA Guidance*

The FDA's "*Guide to Inspections of Quality Systems*,"[2] August 1999, lists CAPA as one of the seven areas for compliance review. Under the chapter dedicated to CAPA, the Purpose and Importance section states:

> *"The purpose of the corrective and preventive action subsystem is to collect information, analyze information, identify and investigate product and quality problems, and take appropriate and effective corrective and/or preventive action to prevent their recurrence. Verifying or validating corrective and preventive actions, communicating corrective and preventive action activities to responsible people, providing relevant information for management review, and documenting these activities are essential in dealing effectively with product and quality problems, preventing their recurrence, and preventing or minimizing device failures. One of the most important quality system elements is the corrective and preventive action subsystem."*

While FDA's QSIT has included the requirement for CAPA since 1996, still today the drug Good Manufacturing Practices (GMPs) (21 Code of Federal Regulations (CFR) Parts 210 and 211) do not spell out this requirement. The main reason for this omission is not that FDA believes such a requirement would not be useful; it is more that the current version of the drug GMPs was released in 1980 without any major revision thereafter.

However, in the proposed amendment of 1996, the requirement was included. It is also being included in the new draft guide, "*Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations* (cGMP),"[3] released by FDA for comment in September 2004. Section D – Evaluation Activities, describes CAPA as: "A key component in any quality system handling nonconformities or deviations." The investigation, conclusion, and follow-up should be documented. The FDA expects corrective actions, which are the "follow-up"

required in CFR 211.192.

An employee may detect discrepancies during any stage of the process or during quality control activities. The establishment of a discrepancy investigation process becomes critical when a discrepancy is found that affects product quality. (cGMP also requires this; see § 211.192.)

Corrective action is a reactive tool for system improvement ensuring that significant problems do not recur. Both quality systems and the cGMP regulations emphasize corrective action. Quality system approaches call for procedures to be developed and documented that ensure that the need for action is evaluated relative to the possible consequences, that is, the root cause of the problem is investigated, possible actions are determined, a selected action is taken within a defined timeframe, and the effectiveness of the action taken is evaluated. It is essential to maintain records of corrective actions taken." (See § 211.192.)

➤ *Regulatory Consequences*

FDA Warning Letters (WLs) are frequently issued because companies do not have an implemented CAPA program or do not follow the existing system. CAPA non-compliance is among the top three reasons for FDA citations. The following are excerpts from FDA-483 observation reports published in the newsletter, "GMP Trends,"[4] that illustrate frequently cited CAPA related non-compliance.

➤ *Laboratory Controls*

> *"…Corrective actions you committed to in your response to the FDA-483 issued…concerning data maintenance and security in laboratory instruments have not been completed. For example, you committed to assess other critical instrumentation, and that individual action plans will be developed as appropriate. However, your laboratory does not maintain the raw data obtained from your laboratory equipment. These systems have not been assessed and you have not developed the individual action plans necessary to bring these systems into compliance."*

➤ *Manufacturing Controls*

> *"…The investigations related to microbial contamination detected in several samples from the capsule manufacturing areas did not address adequately the source of the contamination and the corrective actions necessary to prevent recurrence. Pathogenic organisms and coliforms have been detected in nine different instances in manufacturing equipment, rinse water and the environment. The investigations are inconclusive regarding the source of the contamination, with sample handling listed in five of the nine instances as the possible cause of the Out-of-Specification (OOS) results."*

➤ *Active Pharmaceutical Ingredients*

> *"… In the manufacture of Active Pharmaceutical Ingredients (API's), the firm failed to maintain/replace deteriorated manufacturing process equipment, reactor trains and piping at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality or purity beyond the official or established requirements. For example:*
>
> *a. "The firm's short-term corrective actions, such as increased manufacturing equipment maintenance and repair, and increased visual inspection of the drug product, have not corrected the problem. Inspectional review of the most recent batch of…revealed that many black specks and flakes were detected in the intermediate…crude. Manufacturing Deviation Report (MDR)… identified the problem as another condenser failure.*
>
> *b. "The firm concluded in Manufacturing Deviation Report (MDR)… that long-term corrective actions would require replacement of entire reactor trains and condensers. Condensers were identi-*

fied as the major source for particle shedding. Condensers are currently used in several of the reactor trains, which are used to manufacture at least sixteen different API's, including eight API's sold for use in parenterals."

ISO/IEC 17025

The ISO/International Electrotechnical Commission (IEC) standard, "*General Requirements for the Competence of Testing and Calibration Laboratories*,"[5] has several sections on corrective and preventive actions, for example, section 4.10.1 states:

> *"The laboratory shall establish a policy and procedure and shall designate appropriate authorities for implementing corrective action when nonconforming work or departures from the policies and procedures in the quality system or technical operations have been identified."*

The standard also suggests that a root cause analysis of the problem be determined. "The procedure for corrective action shall start with an investigation to determine the root cause(s) of the problem."

The need for preventive actions is stated in section 4.11.1:

> *"Action plans shall be developed, implemented, and monitored to reduce the likelihood of the occurrence of non-conformances and to take advantage of opportunities for improvements."*

CAPA as a Tool for Continuous Improvement

CAPA is a fundamental management tool that should be used by everybody for on-going quality improvement. The program provides the process for implementing, evaluating, and documenting corrective or preventive actions. The result of the effort should be a well-documented investigation and solution to quality problems that will satisfy not only regulatory requirements, but also will form the basis for effective, continuous improvement.

POTENTIAL SOURCES OF QUALITY PROBLEMS

Each company must decide on the quality problems to be included in a CAPA program. Creating general criteria for screening quality problems would facilitate correct decision-making parameters for considering the initiation of a CAPA process. Quality records represent the primary inputs to any CAPA subsystem. Records retain information after the fact.

An early step in designing a CAPA system is the identification of the key suppliers to the system. All quality systems have some quality subsystems. The subsystems encompass activities from the satellite supplier to the CAPA system. For instance, think about API manufacturing companies. At a system level, a CAPA sub-system must include the following satellite suppliers as defined by the noted sections of the International Conference on Harmonization (ICH) Q7A:

2 Quality Management
3 Personnel
4 Buildings and Facilities
5 Process Equipment
7 Materials Management
8 Production and In-Process Controls
9 Packaging and Identification, Labeling of APIs and Intermediates
10 Storage and Distribution
11 Laboratory Controls
12 Validation
13 Change Control
14 Rejection and Reuse of Materials
15 Complaints and Recalls
16 Contract Manufacturers (including Laboratories)

Data

Quality data that typically require a CAPA process could be classified according to the source origin, in two categories: internal data and external data.

➤ *Internal data*

This group comprises corrective action items gleaned from:

- Information resulted from self inspections (internal audits)
- Internally identified problems:
  - ✓ Quality Control (QC) generated data related to raw materials, intermediates, and finished product quality (e.g. OOS results, trends)
  - ✓ Data related to process and product (deviations, reworked batches, non-conforming product, validation)
  - ✓ Training records
  - ✓ Change control data
  - ✓ Management reviews
  - ✓ Observations by employees
  - ✓ Statistical Process Control (SPC) charts
  - ✓ Trends charts (Pareto or Run charts) and periodical reports
  - ✓ Equipment maintenance reports
  - ✓ Equipment calibration record
  - ✓ Supplier assessment reports

For the preventive loop, inputs could also include:

- ✓ Engineering change requests and engineering change notes
- ✓ Deviation requests
- ✓ Change requests
- ✓ Risk management records (Pharmaceutical Failure Mode and Effects Analysis (PFMEA), Device Failure Mode and Effects Analysis (DFMEA), or Fault Tree Analysis (FTA)
- ✓ Process run charts, process capability index data (CpK or Cp), other SPCs

➤ *External data*

This group comprises:

- Information resulted from external audits (audit and non-conformity reports issued by regulatory authorities or customers)
- Complaints, returned products, customer feedback

WHERE DOES CAPA START?

Once the source of quality problems and the corresponding systems that manage those problems are identified, the next question is "where do the quality systems that feed into CAPA end, and where does CAPA start?"

Looking again at the potential inputs for a CAPA program listed in the previous section, in most cases, the quality problems are documented in the corresponding systems on specific forms, e.g.: audit findings on Non Conformance Reports (NCRs) or audit reports, OOS results onto OOS investigation reports, change requests onto change request forms, training records on specific training forms, trends as statistical interpretation, etc.

After the assessment of the issue, there are two possible situations: 1) no further actions are necessary or 2) further activities are required to help identify corrective actions to prevent recurrence.

In the first case, the conclusion of the final report will clearly state that no follow-up (CAPA) is needed. In the second scenario, root cause analysis, corrective actions or preventive actions, and effectiveness assessment are indicated.

For instance, the final audit report identifies nonconformities and not only observations. The responsible department affected by the quality issues would conduct an in-depth failure investigation based on risk assessment to determine whether the problem(s) is systemic: to implement efficient measures meant to correct problems with immediate corrective action, to correct in order to prevent repetition by way of corrective action, or to prevent the occurrence of potential problems by way of preventive action.

Correction of nonconformities must be followed by in-depth investigation to prevent recurrence. Here starts CAPA. A Corrective/Preventive Action Request (C/PAR) marks the beginning of CAPA.[6] Risk

assessment and root cause analysis, as part of the investigation, will enable the identification of corrective or preventive actions that succeed in addressing the actual problem rather than merely its symptoms.

ATTRIBUTES OF A GOOD CAPA PROGRAM

A CAPA program should be SMARTER: specific, measurable, attainable, results-oriented, time-based, evaluated, and reviewed. All seven attributes of a SMARTER program are equally important. If performance criteria and established metrics (measurable actions) do not exist for analysis and monitoring, program effectiveness cannot be evaluated. The purpose of this section is to present some of a CAPA program's attributes from the perspective of personal experience, recommending as excellent complementary reading, the article[7] by Larry Nold, published in the *Journal of GXP Compliance*, presenting his views regarding a SMART CAPA.

Prevention

A successful quality system could be described as a well-coordinated mechanism that functions as a unique organism: the more complex the quality system, the more difficult it may be to reach the goal. An ideal CAPA program should prevent the identified problem from ever recurring. In practice, things are more problematical and companies may have limited choices when the correction of a quality problem involves financial resources that the company cannot afford. One choice is to keep the problem under control without eliminating it completely, for instance, by increasing the frequency of testing, establishing and following a more stringent monitoring program, etc., all of which help to avoid extreme solutions, such as failing to do anything or spending large sums of money that would end in company closure. This type of choice makes the design of an attainable (reasonably feasible and at the same time, efficient) CAPA program so important.

Timing

Why is timing important? Timeliness is required for every other quality system not only for CAPA systems. A good CAPA program integrates all other quality subsystems. The output of quality problem management (deviations, OOS results, complaints, returned goods, trends, etc, as presented in an earlier section) is input for CAPA, the subsystem meant to ensure in-depth insight into the addressed problem and correct the root cause to prevent repetition. The output of CAPA opens doors for improvements.

Moreover, from a documentation perspective, setting deadlines for each component of CAPA ensures an organized flow of data, avoiding disturbances at all levels of the quality system. For example, if there is a delay in completing CAPA for assessed out-of-trend results, the information may not be available in time for the issuance of the stability report, for periodical review by management, and finally, for inclusion in the Annual Product Review (APR). A postponement could also have undesirable impact on a regulatory submission or on the issuance of responses to a Regulatory Body observation regarding filing documentation.

Review and Evaluation

Considering CAPA a subsystem that realizes a "closed loop" means that all steps are defined and followed to ensure CAPA completion and that, at the end, top management evaluates and reviews the outputs of the CAPA subsystem: evaluation after implementation to determine effectiveness, and periodical review to determine the status of the company's quality system and potential improvement opportunities. The quality loop cannot be considered closed until the CAPA program is reviewed and its effectiveness verified and monitored.

ASSIGNING RESPONSIBILITY FOR IMPLEMENTING THE CAPA PROGRAM

The pharmaceutical industry is dynamic and demanding, requiring top management commitment to continuous improvement ensuring the efficient manufacture of safe products in conformity with the CGMP regulations and related guidelines and guidance. Essential in a CAPA program is management commitment and team building. The responsibility for the CAPA program is shared among executive

managers (organized as a Quality Council or Quality Steering Committee), the Management Representative (MR), process owners, and the CAPA team.

Senior Management

Senior management (executive or C level management) is the first line called to take the initiative and set healthy bases for company quality systems. A top-down approach to quality systems or subsystems generally guarantees a good start. As a Quality Manager, how do you convince company management of the validity of such a point?

In the draft guidance, released for comment on September 2004 – "*Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations*," Chapter IV. A - Management Responsibilities - emphasizes well known and recognized management principles and clearly shows the FDA's current view on executive management level involvement in the matter: "In a robust, modern quality system, senior management demonstrates commitment to developing and maintaining their quality system." There is no doubt that management of pharmaceutical companies must commit to quality and, moreover, provide leadership.

➤ *Obtaining Commitment*

It is not easy to obtain management commitment to the implementation of a new quality system and from a manager's perspective, questioning the appropriateness of a new subsystem like CAPA, is legitimate. Such a project involves additional resources, money, etc. But terms such as, efficiency, cost reduction, complaint reduction, and customer satisfaction increase, catch the attention of any manager. Compliance managers must be persuasive and make effective use of these arguments.

First of all, the Compliance Manager must make it clear to management that quality systems are not a burden or merely a compliance requirement. To the contrary, these ideals support the company's business interests. This is the position FDA expressed in the aforementioned guideline and which appears in the following statement:

> *"Leadership is demonstrated by aligning quality system plans with the manufacturer's strategic plans to ensure that the quality system supports the manufacturer's mission and strategies."*

By itself, this is just another statement. How is it possible to turn this dream to reality?

Be prepared with flowcharts that show the interrelationships between quality systems, how the information flows, and how it can be running smoothly and lead to the expected output, such as under control processes, timely correction of quality issues, and preventing rather than correcting problems. In short, show management that a CAPA subsystem supports the company in achieving its objectives by being a reactive and proactive tool that corrects problems and prevents the occurrence of potential problems, instead of passing through the painful, costly, and cumbersome process of existent problem remediation.

➤ *Management Responsibilities*

Once past this difficult test, management's role begins with organizing and planning, as indicated in the draft recommendation and through well-known business practices:

> *"Senior managers set implementation priorities and develop action plans. Managers can provide support of the quality system by:*
>
> - Actively participating in system design, implementation, and monitoring, including system review (See Chapter IV. A. 5.)
> - Advocating continual improvement of operations and the quality system
> - Committing necessary resources"
>
> *"Managers have the responsibility to communicate employee roles, responsibilities, and authorities within the system and ensure that interactions are defined and understood."*

This is a self-explanatory requirement of the draft guidance.

A comprehensive list of senior management responsibilities could include:

- Commitment to the development, monitoring, and improvement of the quality system
- Setting performance management objectives strategically aligned to company objectives
- Use of quality planning to identify resources and define methods to achieve company quality objectives
- Appointment or hire of a quality systems manager to ensure support by the three means shown above
- Ensuring that roles and responsibilities are properly assigned, communicated, and understood for all individuals involved in the CAPA program
- Performing system reviews as a key component to ensure system continuity, suitability, adequacy, and effectiveness

Management Representative

As the draft guidance recommends, "An organization also has the responsibility to give the individual who is appointed to manage the quality system the authority to detect problems and effect solutions. The analysis and evaluation of well established metrics during periodical management reviews is the vehicle that facilitates the identification of preventive actions as a tool of improvement. Usually, a senior manager administers the quality system and can, thus, ensure that the organization receives prompt feedback on quality issues."

In ISO terms, the executive manager responsible for the management of quality systems and for communicating results during periodical management reviews is called the Management Representative (MR). The MR should report directly to the President or Chief Executive Officer (CEO).

Process Owners

The MR must identify the process owners who typically are the managers of the quality-related departments. The process owners represent an intermediate level of decision-maker between team members and the MR.

CAPA Team

A cross-functional team is made up of individuals who represent quality departments or functional areas within the organization. Team leaders and team members have diverse skills and experience, but should be guided by the same objective. Each member must understand his or her specific role on the team. Responsibilities should be updated because systems mature and the organization will evolve. Team members must be instructed that the new system is part of an overall strategy that ensures efficient business practice and regulatory compliance, as well as securing the future of the business and, ultimately affecting the individual worker's job security.

EVIDENCE DEMONSTRATING CAPA'S PART IN THE SYSTEM

Although documentation and evidence presented will vary in each specific case according the unique processes and products of a company, evidence might include:

- Procedures for management reviews that contain standard agendas with headings that discuss the review of corrective and preventive actions
- CAPA analysis reports submitted for management review
- Agendas relating to the management review of the quality system including corrective and preventive actions and proof that reviews have been conducted
- Schedules of management reviews (past and future) and written reports or minutes that document the meeting, discussions, results, and decisions resulting from those reviews
- Closed, escalated corrective actions and identified preventive actions that resulted from the management reviews

In the course of an inspection, an FDA investigator may seek information on how a particular nonconformity was detected. Under some circumstances, this could lead to requests for information relating to internal audits, supplier audits, and management reviews. Firms should develop an internal policy and procedures to handle these requests. Internal audits, supplier audits, and management re-

views are not typically shared with an FDA investigator. One solution includes issuing official reports, condensed for the purpose. These summaries should be written in appropriate language acceptable for presentation to those outside the gates of the company.

CONCLUSION

At a minimum, an efficient CAPA system should be able to accomplish the following:

- Identify all quality problems and investigate those selected based on screening criteria
- Identify and investigate adverse trends related to process, product, quality system, and customers using statistical methods, and risk analysis
- Prioritize quality problems for investigation based on their significance and risk level
- Allow the traceability of all quality problems that feed into CAPA (audit findings, nonconformities, Out-of-Specification or out of trend results, deviations, customer complaints, etc.), relating corrective and preventive actions to root causes
- Address quality problems from both a reactive and a proactive point-of view
- Produce reports providing information of C/PAR status, cycle time reporting
- Produce effectiveness verification that links to specific root causes; documentation that implemented corrective actions and effectively addressed root causes
- Monitor CAPA metrics and CAPA effectiveness
- Exhibit the capability to incorporate changes and improvements using the company change control system ❑

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Article Acronym Listing

API	Active Pharmaceutical Ingredient
APR	Annual Product Review
C/PAR	Corrective/Preventive Action Request
CAPA	Corrective and Preventive Action
CEO	Chief Operating Officer
CFR	Code of Federal Regulations
cGMP	Current Good Manufacturing Practice
DFMEA	Device Failure Mode and Effects Analysis
FDA	Food and Drug Administration
FTA	Fault Tree Analysis
GMP	Good Manufacturing Practice
GXP	Good Clinical, Laboratory, and Manufacturing Practice
ICH	International Conference on Harmonization
IEC	International Electrotechnical Commission
ISO	International Organization for Standardization
MDR	Manufacturing Deviation Report
MR	Management Representative
NCR	Non Conformance Report
OOS	Out-of-Specification
PFMEA	Pharmaceutical Failure Mode and Effects Analysis
QC	Quality Control
QS	Quality System
QSIT	Quality System Inspection Technique
SMARTER	Specific, Measurable, Attainable, Results-oriented, Time-based, Evaluated, Reviewed
SPC	Statistical Process Control
WL	Warning Letter

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How To Set Up A CAPA Program From Scratch

PART II OF A TWO-PART ARTICLE

*By **Gabriela Bodea***

Part I of this article, "What Companies Should Know and Consider when Designing a CAPA System," introduced the reader to the multiple facets of Corrective And Preventive Action (CAPA) as a fundamental quality subsystem and pointed out the various factors to be considered for the development of a CAPA program. Part I of this article appeared in the July 2005 issue of the Journal of GXP Compliance, Volume 9 Number 4.

ESTABLISHMENT AND DOCUMENTATION OF A CAPA POLICY

When developing a CAPA program, a controlling policy must be in place either as a standalone document (policy) or incorporated into the Quality Manual. A policy is a controlled document that typically includes: title, purpose, mission, scope (all quality subsystems that feed into CAPA), and responsibilities. Depending upon the organizational structure of CAPA within each company, a CAPA system is the responsibility of top management constituted into a quality council that includes all managers with executive functions along with a CAPA administrator. The policy is the base upon which the system is to be built.

A CAPA system is a quality improvement vehicle that is the basis of both reactions to deficiencies and of proactively addressing the prevention of deficiencies. The controlling policy for the system should establish the foundation for this quality improvement vehicle. A CAPA policy should emphasize the active involvement and support of top management and the need for recruiting and assigning a Management Representative (MR) responsible for quality system management. The MR should report directly to appropriate executive management.

IDENTIFICATION OF KEY SUPPLIERS

The Corrective Action (CA) request process should be initiated whenever a quality problem warrants an investigation to determine whether corrective or preventive action is required. The first step toward completing a CAPA request is to understand the key or satellite suppliers. All quality systems have some quality subsystems. The subsystems comprise satellite suppliers to CAPA. The information provided by these sources becomes the input to the CAPA system. Capturing the data electronically will make it easily available when CAPA is launched.

Quality data that typically requires CAPA, classified according to the source origin, include:

- Internal data
  - ✓ Information obtained from internal audits
  - ✓ Information resultant from internally identified problems
- External data
  - ✓ Information obtained from external audits (audit and non-conformity reports issued by regulatory authorities or customers)
  - ✓ Data resultant from complaints, returned products, and customer feedback

Refer to Part I of this paper, section two, "Potential Sources of Quality Problems," (found on pages 61 and 62 of the July 2005 *Journal of GXP Compliance*), wherein is provided a detailed presentation of the quality problems that should be analyzed to determine whether CAPA is warranted.

PLANNING: THE PROJECT DEVELOPMENT PLAN

It is well known that the success of a program is impacted by the effectiveness of its project planning. Planning is mandatory for the success of a CAPA program's design and implementation. Planning a CAPA program is a complex project, especially when CAPA system use is intended to extend to other locations including users from multiple facilities of the company. A written plan, in the form of a controlled document that has been reviewed and approved by corresponding, responsible parties from each location, should be the starting point for the realization of a CAPA system or any improvement to an existing one.

The Institute of Electrical and Electronics Engineers' (IEEE) "Standards for Software Project Management Plans, 1058-1998," and the International Organization for Standardization's (ISO) "Standard 12207, Software Life Cycle Processes," are two sources that were considered during the design of the model of Project Development Plan template proposed below:

TEMPLATE: PROJECT DEVELOPMENT PLAN

Introduction

➢ *Purpose, Scope and Objectives*

The policy includes the mission, vision, and objectives of a CAPA program.

From the very beginning it is essential to clearly establish the kind of CAPA system management has decided to implement or improve: paper-based or electronic, due to the major differences between the two categories. CAPA involves all quality-related structures of an organization. CAPA procedures affect all those structures, from research and development to customer support and any quality activity in between. Because of its far reaching affect, when considering an electronic system, it is crucial to look for CAPA software with at least two essential features: ability to integrate all key supplier systems and compatibility with all other software within the company. The final target is an integrated electronic record management module that generates a traceable record of all elements taking part in CAPA (structures, teams, outputs, documents, etc.).

The purpose of either the electronic or paper-based program is to provide the organization with an efficient CAPA system that will integrate all other quality systems of the company in an effort to ensure that quality problems are accurately identified, investigated in a timely manner, and effectively corrected. Appropriate and effective measures should be implemented to prevent recurrence. Thus, by itself, the CAPA system constitutes a valuable improvement tool.

The scope of the system involves senior management, Quality Assurance (QA), all quality-related departments within the organization, and IT. The scope should also include a description of what is outside the purpose of the system.

References

A list of all documents and other sources of information (scientific literature, industrial guidelines) referenced in the plan should be provided.

Guidance for industry and guidelines, along with industrial practices, should be referenced to justify the need for a CAPA system or for an improvement to such a system. At post implementation, during the monitoring phase, regulatory trend reviews are a must to maintain the compliance status of CAPA as a quality system in the context of a changing regulatory environment.

Standard Operating Procedures (SOPs) are of prime importance for this project. All components of a CAPA system should be formalized and controlled by SOPs. A proposal for a CAPA SOP is provided (see *Figure 1*). A CAPA SOP incorporates all the steps and sub steps in the process of addressing quality problems once the CAPA program has been implemented and delivered. SOPs should be written

Figure 1

CAPA SOP

CAPA STEP	CAPA SUBSTEP	RESPONSIBLE
Analysis (Quality problems feeding into CAPA)	**1. Quality Records Review** A. Audit and Nonconformity Reports - Audit findings review - Systemic analysis B. Other Quality Problems - Screen in conformity with defined criteria to determine the need and level of further actions	QA Audit Manager QA Manager
	2. C/PAR Initiation	QA Audit Manager, QA Manager, or affected Department Representative
	A. C/PAR Log into system - C/PAR Routing	CAPA Administrator
	B. C/PAR Review to identify whether CA or PA is warranted C. C/PAR Approval or rejection	QA Audit Manager or QA Manager
	D. C/PAR Tracking	CAPA Administrator
	3. C/PAR Processing – manual or electronic A. Risk Assessment B. Root Cause Analysis C. Development of C/PA Plan D. C/PA Plan review and approval - Determine whether escalation is needed	 QA and Department Manager MR or Quality Council Assigned Responsible MR or Quality Council
Implementation, Monitoring, and Control	**1. Execution of C/PA Plan** as it was approved, using change control procedure for the approval of all changes to documents or for creation of the required documents; monitoring of implemented solutions; data collection and analysis; and validation of implemented actions	Assigned Responsible or designated team member Assigned Responsible, Team Leader, and Department Manager
Verification	**1. Effectiveness Verification** A. Review and sign off the documents (new or revised) as required by the C/PA Plan - Determine whether escalation is needed B. CA effectiveness verification C. CA implementation approval D. Quality Council Meeting to identify required PA	 QA Audit Manager or QA Manager QA Audit Manager, QA Manager, and MR MR MR
Review	**1. CA Results review at MR request to identify PA** **2. Periodic review of CAPA reports and status** **3. Disposition** **4. Resource allocation**	Top Management/Quality Council

to document all aspects important for the implementation and maintenance of an efficient CAPA system, e.g.: procedures on how to conduct risk assessments and root cause analyses, procedures on periodical Corrective Action (CA) results, review and effectiveness verification, etc.

Project Organization

➢ *Internal Structure*

Describe the internal management structure of the project, as well as how the project relates to the rest of the organization. Include employees and eventual contract staff that will be part of this project and how the staff will be organized and supervised.

Organizational charts to show the structures and functions that are involved in the project and the top down hierarchy, from the senior executive to the team members, are helpful.

➢ *Roles and Responsibilities*

Responsibilities should be assigned to each major role in the project, and the individuals responsible for those functions and activities should be identified. Key players on this project are represented by:

- **Senior (executive or top) Management** is the first line called to take the initiative and set a healthy basis for the company's quality systems. Executive management issues the policy that, as mentioned earlier in this paper, is the base upon which the CAPA system is built.
- **Management Representative (MR)**. According to the draft guidance recommendation: *"an organization also has the responsibility to give the individual who is appointed to manage the quality system the authority to detect problems and effect solutions. Usually, a senior manager administers the quality system and can, thus, ensure that the organization receives prompt feedback on quality issues."*
- **Process Owners.** The MR will identify the process owners who typically are the managers of the quality-related departments. The process owners represent an intermediate level of decision-making between the team members and the MR.
- **CAPA Team.** This cross-functional team is made up of individuals who represent quality departments or functional areas within the organization. Team leaders and team members should have diverse skills and experience and be guided by the same objectives. IT representatives play an important role, particularly during the implementation of an electronic CAPA system.
- **CAPA Administrator** is one of the team members who has been assigned the overall responsibility for the system.
- **Contractors and Consultants** could be involved, depending on the magnitude of the project and company policy.

Process Plans

➢ *Start-up Plan*

Describe how the project effort, cost, and schedule will be estimated.

Example: Experience with the existing CAPA program showed clearly that the program does not meet the desired performance, but we are not aware at what level all problems exist.

Gap analysis should be performed to determine the correct course of action. Gap analysis is a comparison of the existing system, support documentation, and resources with defined requirements, e.g.: references to be considered, existing standards, or internal customer (departments involved in quality activities) expectations.

Implementation and maintenance of the CAPA system is a regulatory requirement, as indicated in Part I of this paper. For the purpose of gap analysis, and in addition to the regulatory requirements (Food and Drug Administration (FDA), ISO), comparison should be made with industrial standards, information offered by Warning Letters, previous experience, and references expressing authorized points of view (e.g.: FDA officials, representatives from professional organizations, etc.).

Describe how staffing will be done, along with the expected level of staffing by project phase, types of skills needed, and sources of staff (may be employees or contract personnel). For any resources needed in addition to personnel, such as hardware, facilities, service contracts, and soft-

(Continued on page 197)

Figure 2

CAPA PROGRAM STEPS

Step	CAPA Fundamentals	Software Specific Aspects
1. Policy	CAPA policy should emphasize the active involvement and support of top management and the need of recruiting and assigning a Management Representative (MR) responsible for Quality System management. The MR will report to appropriate executive management. The policy is the base upon which the system is to be built and should be communicated across the company.	Idem
2. Identification of Key Suppliers	All quality systems have some quality subsystems. The subsystems comprise satellite suppliers to the CAPA program.	Idem
3. Planning	The CAPA program should be viewed as an addition of new procedures and forms to the subsystems that feed into CAPA (in companies that document quality occurrences on specific templates, e.g., OOS Result Investigation Report, Deviations and Nonconformity Report, Stability Report, etc.) or as an improvement to existing subsystems (in medical device or ISO certified companies). A Program Development Plan should be written, approved, and controlled. The result of the planning phase should be a clear understanding of what is needed and how the company will succeed at implementing an efficient CAPA system. An in-house training plan should be approved and executed. Separate, specific training programs are recommended for upper management and staff respectively. Key deliverables resulting from the planning process should be identified.	Gap analysis is the mechanism for identification of improvement opportunities to be implemented into the automated CAPA system, based on experience with the paper-based system. CAPA software must be able to integrate all key supplier systems and, therefore, be compatible with the other computerized systems that provide input data for CAPA, e.g.: LIMS, documentation management system, audit management, calibration management, etc. The software must be validated to comply with 21 CFR Part 11. Many factors must be considered during this phase so that an optimal solution results. The final software, either an existing one to be upgraded or new software, must be suitable for the company's intended applications. The supplier of software will provide user training and technical support. In-house training plans will be developed for legacy software.
4. Role of Automation in a CAPA System	Assessment of qualification, need for infrastructure, and software and application's validation.	Risk-based validation of CAPA software is recommended initially at installation, after changes (e.g., updates) that impact the validation status, or when system reviews or regulations changes indicate

Step	CAPA Fundamentals	Software Specific Aspects
		that the extent of qualification or validation may need to be changed.
5. Team Building	The organizational structure should include a cross-functional team with established roles and responsibilities to ensure the success of a CAPA program.	The structure of the team will be different due to specific features of an automated program, but the principles are the same. IT representative will be a team member, providing technical support (software and infrastructure installation, qualification, maintenance, etc).
6. CAPA SOPs	During the implementation phase, before the system becomes effective, the SOPs will be adjusted. If this is the beginning of the implementation of a CAPA program within a company, many changes will be made and additional instructions will be included in the SOP based on practical experience and lessons learned.	Writing effective procedures prior to automation is key as well.In most of the cases, if not always, companies decide to implement an automated system after years of experience with a paper-based quality management. The past experience is valuable, helping in the development of a good procedure that will require minor modification during the implementation phase of an automated system. Effective manual procedures do not necessarily translate into automated procedures. Automation most often helps streamline processes and may result in the elimination of steps that may be appropriate in the manual world, but are unnecessary in the world of automation.
7. Implementation	During the transition from paper-based records to an electronic format, keeping paper copies is critical for remaining compliant during implementation, in that phase when the automation system is not yet in place. A strategy for implementation should follow the requirements of the approved Project Development Plan.	In cases involving multiple facilities or locations or for multinational organizations, start within a single business unit, as a pilot project. Developing a system for global use that has been optimized locally implies risks in terms of security, intellectual property protection, successful collaboration environments, etc. The commonly used means for this type of development is the Internet; the CAPA system will be Internet based. The implementation strategy avoids some of the many steps and communications involved in a paper-based CAPA system due to the ability of well designed software to launch step after step according to a pre established workflow and to send alert notifications in case of missed steps, deadlines overdue, etc.
8. Effectiveness Measurement	The program must meet the established objectives. The ability of a CAPA system to “learn” from past mistakes allows for the design of focused improvement efforts directed toward chronic or systemic root causes (Preventive Action).	Idem

(Continued from page 194)

ware, describe the plan for acquiring those resources.
Describe any training that will be needed for CAPA implementation, in both technical and managerial skills. For managers and directors, one training session comprising a high level overview, regulations overview, benefits of regulations, and consequences of non-compliance is enough. Include a schedule for the training to be provided, number of people to be trained, and how the training will be conducted.

An in-house training plan should be executed as it was approved and should include:

- Training needs assessment for team members according to their roles (roles and responsibilities attributed to the functions defined in CAPA draft SOP)
- Plan development
- Plan implementation
- Training efficiency evaluation
- Training documentation

➢ *Work Plan*

Specify the work activities and their relationships depicted in a work breakdown structure. Decompose the structure to a low enough level to facilitate sound estimating, tracking, and risk management. Work activities should detail the approach, needed resources, duration, and acceptance criteria.

- **Schedule**
  Specify the schedule for the project showing sequencing and relationships between activities, milestones, and any special constraints.
- **Resource Allocation**
  Identify the resources associated with each of the major work activities as well as an overall summary of the resource loading for the project.
- **Budget Allocation**
  Estimate the budget for each of the major work activities. Use the organization's standard cost categories such as personnel costs, equipment, and administrative support.

➢ *Control Plan*

Describe how the project will be monitored and controlled. In this respect, activities like continual progress monitoring, team reviews, formal progress reviews, change management, and plan review will be part of the control plan. The company's change control system will be used for impact analysis of proposed changes, and for approving changes, monitoring implemented solutions, data collection and analysis, as well as validation of implemented actions.

• Schedule Control

Describe how progress will be monitored and controlled. Address how the schedule will be controlled for all items including: milestones, progress to plan activities, and corrective action upon serious deviation from the plan; when reporting will be done for both the project team and management; and what tools and methods will be used.

• Reporting and Communication Plan

Describe the mechanisms, formats, frequencies, and information flow to be used for communicating the status of project work, progress of the project, and other information as needed for the project.

➢ *Closeout Plan*

Describe the plan for closing out this project. Include descriptions of how staff will be reassigned and project materials will be archived, how post-project analysis will be gathered, how lessons learned will be documented, along with the analysis and documentation of project objectives achieved. Include an examination of the initial cost/benefit analysis to see whether objectives have been met. Include knowledge transfer plan.

If this project is to be followed by a next release effort, for instance to other facilities within a corporation, such as operations and maintenance, describe how those efforts will be planned.

Supporting Process Plans

➢ *Reviews Plan*

Describe the processes, techniques, and tools that will be used for verification and validation of the work products and activities. Identify which work products will receive what types of peer reviews, such as inspection and technical reviews, and what roles will participate in such reviews. Identify the types of testing that will be done throughout the life-cycle, and which roles will be involved in each, such as unit testing, module testing, integration testing, system testing, and acceptance testing. For the purpose of verification, objective criteria to be used for acceptance should be included. Roles and responsibilities for reviewing the plan, generating the acceptance tests, running the tests, and reviewing results should be established as well.

➢ *Project Reviews*

Describe the planned schedule for conducting project reviews, who is to be involved, and what procedures will be used for preparing and conducting the reviews. Include reviews that are done for the project team only, for local management, and for any external organizations, such as an acquirer or subcontractor.

- **Process Improvement Plan**
  Describe the activities that will be done to periodically assess the project's processes, identify areas for improvement, and implement improvement plans.
- **Document Control**
  Based on the changes required as part of improvement, the process management plan will be updated through the change control system of the company. The change history will reflect all modifications for each revision.
- **Document Storage**
  Indicate the electronic file where the document and its eventual revisions will be stored.
- **Document Owner**
  Typically, Quality Assurance (QA) or Quality Unit (QU) is responsible for developing and maintaining this document.
- **Appendices**
  Include any relevant additions or supporting documents.

The result of the planning phase should be a clear understanding of what is needed and how the company will succeed in implementing an efficient CAPA system.

Key deliverables resulting from the planning process include:

- Structure of the team, including roles and responsibilities
- Communication at each structure level and among different levels
- Work activities and their relationships
- Schedule and schedule control
- Resources and budget needs
- Activities reporting, control, and verification
- Improvements implementation processes

ROLE OF AUTOMATION IN A CAPA SYSTEM

Well-configured CAPA software should significantly simplify the CAPA process and constitute a failsafe quality management system.

From CAPA initiation to close out, an automated CAPA system should play an essential role at each step, ensuring that all quality problems are identified and addressed through a controlled sequence of events that avoids missing steps or activities. This is accomplished due to the software's ability to automatically begin the next subsystem when one subsystem is completed - until the CAPA loop is closed.

CAPA Initiation

Any authorized user could initiate a CAPA. Users should collect and analyze data according to the nature of the problem. A CAPA Request (C/PAR) may be automatically routed to appropriate departments for initial review and approval. Relevant related electronic files may be attached as reference documents.

Investigation and Root Cause Analysis

Once a CAPA has been initiated, it will follow its assigned workflow process. For instance - the first step after problem verification may be to initiate investigations to properly identify the root cause of the problem. The software should link investigation records to the parent CAPA record, facilitating root cause analysis of the problem, provide full follow-up and tracking of investigation assignments and due dates, manage the investigation workflow approval

process, provide notifications, alerts, and escalations of overdue investigations.

CAPA Plan Issuance and Approval

A CAPA plan should be created and routed for approval. The CAPA plan should be routed for approval using a serial or parallel approval process including required signatures and optional signatures.

Moreover, the system should be capable of producing CAPA traceability reports, which relate corrective and preventive actions to root causes.

The records should be routed for approval via an automated workflow process. The system should verify that all required information has been captured before moving it on to the approval stage.

CAPA Implementation

Once the CAPA plan has been approved, plan implementation can begin. As work is completed, different users should be notified when certain milestones have been achieved, or when they have not been completed within a given timeframe.

By using an electronic CAPA system, follow-up, tracking, and monitoring activities can be automated. Workflow steps such as "In Progress," "Completed," "Verified," "Approved," and "Closed," should be configured specific to the workflow process. Alerts should be issued and appropriate individuals should be notified concerning items falling past due, requiring approval, or verification. Search capability should enable users to quickly find items past due, assigned, etc. The software providing status information, workload distribution, timing, etc., should generate fully integrated reports.

Effectiveness Verification

The software should automatically initiate and schedule effectiveness checks of the implemented CAPA by tracking individual effectiveness checks and links to specific root causes, documenting that corrective actions have effectively addressed the root cause. The software should also monitor and track CAPA success rates and related metrics and communicate changes to the organization via an automated notification process. Reporting tools should allow the design of a wide range of graphical and statistical reports.

Software Installation and Validation

With a paper-based CAPA program, certain data will be generated, edited, captured, and stored on electronic format, mainly as Excel® spreadsheets or formatted MSWord® files, along with the paper copies e.g.: calculations, templates, plans, and reports. Based on the criticality of the application, the risk assessment analysis will indicate the infrastructure and computerized systems that should be subjected to qualification or validation.

Unlike paper-based programs, automatic or electronic systems must be validated. Risk-based validation of CAPA software is recommended initially at installation, after changes (e.g., updates) that impact the validation status, or when system reviews or regulation changes indicate that the extent of qualification or validation may need to be changed.

Typically, the system owner defines the validation steps for the lifecycle phases. For validation purposes, the following steps could be considered: planning, specification setting, vendor assessment (audit or documentation review), installation, functional testing, maintenance, security control, change control, and audits of system and subsystems.

Planning the implementation of an automated CAPA system should address aspects such as: cost-benefit analysis, determination of user and computer numbers, need for audit of supplier according to Good Automated Manufacturing Practice 4 (GAMP 4) guide, and an overall validation plan. A validation plan containing templates, guidelines, and step-by-step procedures for all steps of the validation of the software would definitely assist the planning.

At this stage, end users should be trained on software application(s).

CAPA SOPs

Standard Operating Procedures

SOPs concerning the CAPA system will be written in order to:

- Define how CAPA will incorporate all quality issues. Using a flow chart, CAPA steps may be specified from failure investigation to track the CAPA process and for periodic management review.
- Establish responsibilities for the members of the cross-functional team responsible for conducting the project from remediation planning to verification.
- Define the Root Cause Analysis (RCA) techniques for assessment and identification of gaps in each process.
- Identify the statistical tools, such as Statistical Process Controls (SPCs) to be used for CAPA validation, etc.
- Show documentation flow.

An outline example of a CAPA SOP is presented in *Figure 1.* The corresponding flowchart appears in *Figure 5,* page 64. Looking at the flowchart, it is easy to seize the two loops inside corrective action and preventive action processes.

Note: Comprehensive SOPs that should be written to document CAPA subsystems are not the subject of this paper; however, several milestones are emphasized here.

Glossary of Terms

Due to the complexity of the CAPA concept, a Glossary of Terms can be of real use. The development of a vocabulary will facilitate a good understanding of key elements, making up a common language within the organization and preventing confusion with semantics.

C/PAR

The author proposes a Corrective/Preventive Action Request (C/PAR) template. This is the template to be used for the initiation and documentation of CAPA components (see *Figure 3*). Once the need for CAPA is determined, a C/PAR will be processed in order to identify the root cause(s) of the problem.

The C/PAR template provided follows the steps of the CAPA procedure requiring the recording of all relevant information for a full and correct understanding of the process flow, as follows:

- Type of quality problem (audit nonconformity, deviation, Out of Specification (OOS) result, trending data, training, validation, change control data, complaint, recalled, returned product, or other)
- Description of the problem (specify what is not met or should be met)
- Evidence observed
- Preliminary assessment of potential impact and risk
- Immediate corrective action
- List of possible causes and supporting data
- Analysis results and data (supportive documents attached)
- Root cause analysis
- CAPA plan number
- Plan evaluation and implementation recommended
- CAPA implementation
- Description of implemented actions
- CAPA effectiveness verification
- Quality Council meeting required or not

Risk Assessment

Like CAPA, risk assessment is a regulatory requirement and a valuable instrument for the correct evaluation of the risk that a quality problem represents to the product's quality, the company's quality system, or to the final user of the product.

The FDA draft guidance released on September 29, 2004 - "Guidance for Industry Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations"[1] places the risk management in the large context of a GXP environment:

> *"The concept of risk management is a major focus of the Pharmaceutical cGMPs for the 21st Century Initiative. Risk management can guide the setting of specifications and process parameters. Risk assessment is also used in determining the need for discrepancy investigations and corrective action. As risk assessment is used more formally by manufacturers, it can be imple-*

mented within the quality system framework."

The role of risk management in a Medical Device company's quality system is clearly defined by the FDA in the preamble to the October 7, 1996 Quality System regulation.[2] In one of the comments of the preamble, which relates to the degree of corrective or preventive actions expected, FDA states:

> *"FDA cannot dictate in a regulation the degree of action that should be taken because each circumstance will be different, but FDA does expect the manufacturer to develop procedures for assessing the risk, the actions that need to be taken for different levels of risk, and how to correct or prevent the problem from recurring, depending on that risk assessment."*

The recent draft guidance elaborated by the GHTF Group 3 [3] emphasizes the place of risk management, considering it "an integral part of the quality management system CAPA processes." Moreover, the guidance provides the view of the Group on a risk-based CAPA system. The excerpt that addresses this topic states:

> *"It (risk management) provides the mechanism for determining the severity of items identified in one's specific quality data points (such as complaints, service reports, manufacturing defects, engineering non-conformities, supplier audits, and external/internal audits). The CAPA process combined with risk management output facilitates a closed loop process and may be a measure of the quality system effectiveness."*

Risk management applies to the quality systems of pharmaceutical companies as "members" of U.S. FDA regulated companies and not only to medical device manufacturers.

The category of risk under which the individual cases of nonconformities fall could be determined by evaluating whether the event or nonconformity:

- Affects product, process, customers, or the quality management system
- Requires containment action
- Has system-wide implications
- Has the potential for legal consequences
- Affects company profit margins
- Needs MR decision, etc.

The response to the question, "What quality problems must be addressed with priority compared to the others," will be based on risk. This is a critical issue when the system is burdened with C/PARs due to an inefficient CAPA system or when existing procedures are not followed.

In the case study presented at the end of this paper (see section entitled "Implementation"), the nonconformity does not pose any risk to the patient, but is of major risk from a regulatory perspective, customer dissatisfaction, company image, and automatically, business safety. If the nonconformity is recurrent and not solved, the Regulatory Body could enforce penalties.

Root Cause Analysis (RCA)

A root cause analysis to isolate the cause(s) of the problem may be warranted. The Assignee (individual responsible for implementation) will use his or her best judgment to decide "how deeply" to investigate the problem. This subjective decision will be reached based on the magnitude and severity of the problem. As part of the CA, qualitative and/or quantitative effectiveness criteria for the prescribed action may be identified.

The basic reason for investigating and reporting the causes of occurrences is to enable the identification of adequate or efficient, corrective, and eventually preventive actions, to avoid recurrence and thereby prevent consequences difficult to correct. Bottom line, the RCA should look not only at the issue at hand and how to correct it, but also should ask whether that quality problem is systemic in its nature and should be addressed across the quality system.

CAPA Plan

The assigned representative of the affected department will be responsible for developing a Corrective and Preventive Action plan that could incorporate the sequence of elements on the model of the provided template (*Figure 5*, page 61).

➢ CAPA Plan Template Structure:

- **Date, Number, C/PAR#**
  The CAPA plan will be assigned a date and number. For the purpose of traceability, the number of the C/PAR that documents the quality problem should be referenced. This will facilitate the understanding of the proposed actions included in the CAPA plan.

- **Actions to be Completed**
  A detailed description of the activities and tasks that must be accomplished to either correct the existing problem or eliminate a potential problem should be provided. For a CAPA program to be effective, it is important to take a global approach. Identify all actions that will be required to address everything related to the situation.

- **Document Changes Required**
  List any documents that will be modified and describe, in general terms, what the modifications will be.

- **Procedure, Process, or System Changes Required**
  Management should then review the CA plan to determine whether proceeding with the implementation is acceptable. The QA specialist reviews the proposed CA and determines whether implementation of the CA requires the creation of or revision to a document. The Document Manager will be notified that there will be a new document or a revision to an existing document resulting from the CA. This alerts a watch for this document as a result of the CA and prepares the document staff to review the created or revised document for its effectiveness as part of the CA when it is received.
  The changes should be described. Enough detail should be included so that what must be done is clearly understood. The expected outcome of these changes should also be explained.

- **Training Required**
  Employee training is an essential part of any change that is made and should be part of the action plan. To ensure that the actions taken will be effective, any modifications made to documents, processes, etc., should be effectively communicated to all persons or departments that will be affected.

- **Qualitative and Quantitative Criteria**
  Include a list of metrics to measure success criteria. These could be qualitative, such as, increased customer satisfaction or company 'goodwill,' etc., or quantitative, such as, percent of work accomplished, number of hours needed, number of changes completed, etc.

- **Assignee and Team**
  The structure of the team should be defined, specifying name, department, and position for each member.

Effectiveness Verification

In Part I, section four, "Attributes of a Good CAPA Program," page 63, the author defined and discussed the components of an effective CAPA program and indicated that a CAPA program should be SMARTER: Specific, Measurable, Attainable, Results oriented, Time based, Evaluated, and Reviewed.

Corrective and Preventive Actions may be considered effective when they result in the elimination of nonconforming product, zero complaints, and subsequently, improve customer satisfaction without negative alteration of the company's positive image in the market.

Measuring the effectiveness of implemented corrective actions is a mandatory step of CAPA. This can be realized by comparing the actual results with the performance criteria defined in the CAPA plan. Depending on the nature of the implemented actions, QA/QU should:

- Review the newly generated or updated documentation (e.g.: training records)
- Assess the potential impact of the changes on other systems or documents
- Inspect a subsystem or a monitoring program
- Review customer satisfaction questionnaires
- Analyze quality costs generated by lack of quality
- Review in-process and finished non conforming or rejected product
- Review regulatory and customer audits for potential, critical nonconformities identified

TEAM BUILDING

The organizational structure of a CAPA program should include a cross-functional team with established roles and responsibilities to ensure success. As presented earlier in this article, a CAPA team should include:

- Senior (executive/top) Management
- Management Representative
- Process owners
- CAPA team
- CAPA administrator
- Contractors and consultants
- IT representative(s)

The IT representative will provide technical support (software and infrastructure installation, qualification, maintenance, etc).

This team will apply CAPA procedures to each individual quality problem that will be addressed following the CAPA system.

Many existing CAPA systems suffer from an overly broad distribution of responsibility. A dedicated team should be created so that the team members are devoted exclusively to this effort. The team should be heavily involved with non-conformance triage, investigation, documentation, data system entry, and closure. Such teams work best when they consist of a combination of a) people familiar with the history of current, open non-conformances and the existing CAPA system and b) outsiders able to offer a fresh perspective.

IMPLEMENTATION

The Process Development Plan establishes all elements and sequences of events that constitute an implementation strategy.

The flow of implementation effort should include, at a minimum:

- Availability of all resources identified as needed in the plan.
- Written SOPs: All SOPs referenced in the plan should be ready by the time the project begins. The existence of SOPs is mandatory for both types of systems, either paper-based or (automatic) electronic, but is especially important for the paper-based system. The great advantage of an automatic system is that some of the SOPs are built into the software and the system launches without human intervention into next steps, which is not possible in a paper-based system.
- Team building: selection and training of staff.
- Work activities: In order to verify the suitability, correctness and completeness, and determine the need for improvements, the CAPA SOP will be put into practice. It will be applied, through practical exercises, to all categories of quality problems identified as being key suppliers to the system (refer to section two of this paper, Identification of Key Suppliers). It is within the latitude of each company to decide the magnitude of this exercise so that the newly created or improved CAPA system can be considered validated.
- Review and process improvement plan: According to the plan provisions, the results of all implementation efforts will be reviewed, and consistent with the output of these reviews, improvements within the scope of the plan should be proposed subject to approval.
- Monitoring and control of work and documents or records: The progress of work should be monitored to capture all eventual difficulties and to determine whether the work is on schedule.
- Reporting and communication: The results of work scrutiny and progress will be reported and communicated to all appropriate individuals.

- Team reassignment: A plan should exist for team member reassignment at the end of the project's execution.
- Documents storage: A detailed plan for the storage and retrieval of documentation is required.
- Post project analysis: The execution of the project plan should be followed by a thorough analysis of implementation success and success on reaching the goals of the project. The analysis should include a cost/benefit analysis and an analysis of lessons learned.
- Subsequent efforts planning: When a project is to be followed by a next release effort, for instance to other facilities within a corporation, such as operations and maintenance, describe how those efforts will be planned.

The implementation strategy of an automatic or electronic CAPA system avoids some of the many steps and communication involved in a paper-based CAPA system. This is due to the ability of well-designed software to launch step after step according to a pre-established workflow and to send alert notifications in case of missed steps, overdue deadlines, etc.

A paper or hybrid system cannot ensure the expected efficiency that leads to growth and profitability, but during the transition from paper-based records to an electronic format, keeping paper copies is critical to remaining compliant.

Implementing a CAPA system is not an easy task, especially for companies with multiple locations or within multinational companies. In cases of companies with multiple facilities or locations or with multinational organizations, automation should be first limited to a manageable group. Depending on organizational size, it is best to start this phase within a single business unit as a pilot project.

Developing a global system that has been optimized locally implies risks in terms of security, intellectual property protection, successful collaboration environments, etc. The commonly used means in this case is the Internet; the CAPA system would be Internet based.

I mentioned that a CAPA Plan should require the identification of the need for review and adjustment of existing document(s) or the issuance of new document(s). Changes or creation of a document can be accomplished only by following change control procedures. Multinational companies could have manufacturing facilities in countries regulated not only by the U.S. FDA, but by Canadian, European, Australian, or other regulatory authorities as well. If nonconformity is systemic and affects not only the initiator, but also other facilities from areas with different GMP practices compared with U.S. FDA regulations, then the applicability of the change should be assessed, and the appropriate solutions should be looked for. Closing the loop within a CAPA plan when an open computer system does not exist to ensure the efficient flow of information is an example of how difficult it can be to implement a CAPA program in an international company and of how important communication is between the partner-users of a global CAPA software system.

EFFECTIVENESS MEASUREMENT

Effectiveness is verified for each corrective or preventive action to determine whether CAPA was efficient in eliminating the cause of a particular quality problem to avoid recurrence and also to determine the effectiveness of the program as a whole.

The program must meet the established objectives. If, based on periodic reports, analysis during management reviews, and comparisons with performance criteria, it is concluded that the CAPA program plays the role of a mere data base without reaching the objectives for which it was designed, the program must be improved and corresponding changes should be implemented.

An effective CAPA system guarantees that information regarding the nature and context of non-conformances is captured, documented, investigated, and closed. The ability of a CAPA system to "learn" from past mistakes allows for the design of focused improvement efforts directed toward chronic or systemic root causes through preventive actions. Such concerted efforts can lead ultimately to significant reductions in non-conformance generation, one of the major objectives of a CAPA program. ❑

REFERENCES

1. U.S. FDA, "Draft Guidance: Quality Systems Approach for Pharmaceutical Current Good Manufacturing Practices," September 2004
2. U.S. FDA, "The Good Manufacturing Practice (GMP - Quality System Regulation) Final Rule," Federal Register / Vol. 61, No. 195 / Monday, October 7, 1996 / Rules and Regulations, 52633, pp. 33-34, http://www.fda.gov/cdrh/fr1007ap.pdf
3. GHTF Study Group 3, "Proposed Draft SG3/N15R6 - Risk Management as an Integral Part of the Quality Management System"

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Article Acronym Listing

C/PAR	Corrective/Preventive Action Request
CA	Corrective Action
CAPA	Corrective And Preventive Action
cGMP	Current Good Manufacturing Practice
FDA	Food and Drug Administration
GAMP	Good Automated Manufacturing Practice
GHTF	Global Harmonization Task Force
IEEE	Institute of Electrical and Electronics Engineers
ISO	International Organization for Standardization
IT	Information Technology
MR	Management Representative
OOS	Out of Specification
PA	Preventive Action
QA	Quality Assurance
QU	Quality Unit
RCA	Root Cause Analysis
SOP	Standard Operating Procedure
SPC	Statistical Process Control

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Figure 3

C/PA PLAN (USE ADDITIONAL PAGES AS NEEDED)

Number #	Date:

C/PAR#

Actions to be Completed:

Document Changes Required:

Procedure, Process or System Changes Required:

Training Requirements:

Team Structure	Name	Department	Position
Assignee (individual responsible for implementation/ Process Owner)			
Team Leader			
Team Member			
Team Member			
Team Member			

Qualitative and Quantitative Criteria

Implementation Schedule	
Implementation Deadline	

	Name	Position	Signature	Date
Written				
Reviewed				
Approved				

Figure 4

C/PAR #:

☐ CA
☐ PA

Type of Quality Problem
☐ Audit nonconformity, deviation, OOS result, trending data, training, validation, change control data, complaint, recalled, returned product, other

Description of the Problem (specify what is not met or should be met)

Evidence Observed

Preliminary Assessment of Potential Impact and/or Risk

Initiator's Name Signature Date

Approved:
☐ Yes
☐ No
If No, Justify:

Audit Manager/QA Manager Signature Date

Immediate Corrective Action

List of Possible Causes and Supporting Data

Analysis Results and Data

☐ Supportive Documents Attached

Root Cause Analysis

Assignee Signature Date

C/PA Plan number:

Assignee Signature Date

Plan Evaluation – Implementation Recommended

☐ Yes
☐ No

If No, justify:

QA Manager Signature Date
MR Signature Date

C/PA Implementation

Description of Implemented Actions

Assignee + team
Name Signature Date
Name Signature Date
Name Signature Date

CAPA Effectiveness Verification

Efficient CA:

☐ Yes
☐ No

If No, Justify:

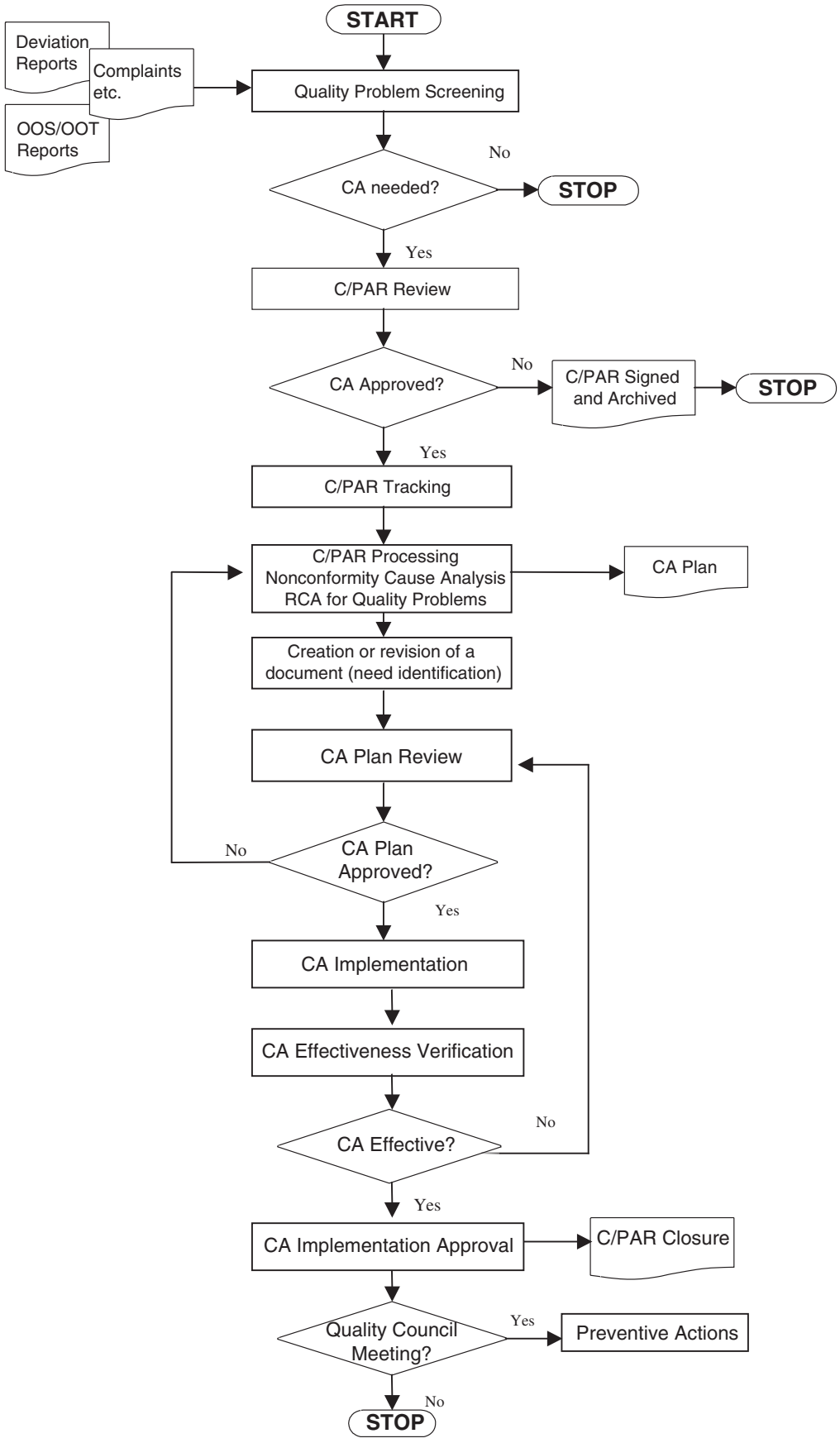
Quality Council Meeting Required:

☐ Yes
☐ No

Audit Manager/QA Manager Signature Date
RM Signature Date

Figure 35

CAPA Plan Structure



Conducting an Internal Audit for Electronic Records Compliance: *A Primer*

The internal audit for electronic records compliance is a management tool designed to measure compliance with the standards, policies, and procedures designed to promote compliance with 21 CFR Part 11.

by
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This article is written to provide guidance for the internal auditor who is, or is thinking about, performing an audit for electronic records compliance. It is written as a primer – a place to start – that the internal auditor can build upon based upon the level of his or her experience. The internal audit for electronic records compliance is a management tool designed to measure compliance with the standards, policies, and procedures designed to promote compliance with 21 CFR Part 11.[1] This regulation provides the requirement to control the creation, modification, maintenance, archiving, and distribution of electronic records and is fast becoming a priority for Industry and the FDA. Company management is consequently devoting an increasing amount of resources – time and money – to achieve compliance. The audit will allow management to (1) determine if the organization is adhering to the standards, policies, and procedures established to promote compliance with the 21 CFR Part 11 and (2) identify the deficiencies that exist vis-à-vis compliance with 21 CFR Part 11.

The Audit Strategy

So where do you start? The answer is: develop an audit strategy; that is, define what you will audit and why. Logically, the basis for your audit strategy should be the document titled *Guidance for Industry: Computerized Systems Used in Clinical Trials*,[2] located on page 17 of this Journal. This document addresses the requirements of 21 CFR Part 11 and its principles are applicable to clinical sites, contract research organizations, data management centers, and sponsors where computerized systems are employed. If the internal audit is designed to map to the provisions of the guidance document at a minimum, the risk that significant issues will be overlooked is small and you can always make the audit more robust.

Audit Conduct

Figure 1 provides the relationship of the provisions of the guidance document to specific audit steps to perform and the impact of any deficiencies noted. The information provided is as follows:

- Guidance document provision: These are the specific

regulatory requirements and/or expectations taken directly from the guidance document.

- Suggested audit steps: There are specific activities to perform (e.g., documents to review, items to look for in the documentation, types of reviews to conduct) to determine if the given requirement/expectation per the guidance document is being met.
- Impact of deficiency (to be included in audit comment): This column provides suggested language to include in the audit comment section of the internal audit report regarding the significance of audit deficiencies (i.e., the regulatory requirements/expectations not met).

Figure 1

Relationship of Guidance Document Provisions to Internal Audit Strategy

Guidance Document Provisions	Suggested Audit Steps	Impact of Deficiency (To Be Included in Audit Comment)
I. INTRODUCTION		
II. DEFINITIONS		
III. GENERAL PRINCIPLES		
IV. STANDARD OPERATING PROCEDURES		
Standard Operating Procedures (SOPs) pertinent to the use of the computerized system should be available on site. SOPs should be established for, but not limited to: ■ *System Setup/Installation* ■ *Data Collection and Handling* ■ *System Maintenance* ■ *Data Backup, Recovery, and Contingency Plans* ■ *Security* ■ *Change Control*	1. Request copy of all formal, approved SOPs. Note that the specific SOP titles may differ from the categories included in the guidance. 2. Determine that the approved SOPs address the issues identified in the guidance document and that they provide a means to confirm compliance. 3. Review applicable compliance procedures to confirm that the approved SOPs are being complied with and that documented evidence exists to confirm compliance. 4. Perform a documentation review to confirm that the documents are available on-site (i.e., wherever the respective processes are being performed).	SOPs provide the methods that management relies upon to help ensure the integrity of the electronic data and the processes that produce and maintain the data. Lack of SOPs, or the lack of SOPs on-site, means that the applicable staff will not have approved procedures to follow to maintain control of the applicable computer systems and electronic data. Lack of documented evidence of compliance increases the risk that controls are weak or non-existent.
V. DATA ENTRY		
A. Electronic Signatures		
1. To ensure that individuals have the authority to proceed with data entry, the data entry system should be designed so that individuals need to enter electronic signatures, such as combined identification codes/passwords or biometric-based electronic signatures, at the start of a data entry session.	1. Review the approved functional specifications to determine if the following requirement is included: electronic signatures must be entered at the start of a data entry session. 2. Review the approved technical specifications to determine if the following requirement is designed and programmed properly: electronic signatures must be entered at the start of a data entry session. 3. Review the test cases and scripts and documented test results to confirm that the following requirement functions properly: electronic signatures must be entered at the start of a data entry session.	An electronic signature is a means to help ensure that only authorized data entry takes place. Unauthorized data entry is a limitation on the integrity of study data.
2. The data entry system should ... be designed to ensure attributability... [E]ach entry to an electronic record, including any change, should be made under the electronic signature of the individual making that entry. *a. The printed name of the individual who enters data should be displayed by the data entry screen throughout the data entry session.*	1. Review the approved functional specifications to determine if the following requirements are included: (a) each entry to an electronic record is made under the electronic signature of the individual making that entry; (b) the printed name of the individual who enters data is displayed by the data entry screen throughout the data entry session. 2. Review the approved technical specifications to determine if the following requirements are designed and programmed properly: (a) each entry to an electronic record is made under the electronic signature of the individual making that entry; (b) the printed name of the individual who enters data is displayed by the data entry screen throughout the data entry session. 3. Review the test cases and scripts and documented test results to confirm that the following requirements function properly: (a) each entry to an electronic record is made under the electronic signature of the individual making that entry; (b) the printed name of the individual who enters data is displayed by the data entry screen throughout the data entry session.	Entry of data by one individual under someone else's name is unauthorized data entry, which is a limitation on the integrity of study data.

Figure 1

Continued

Guidance Document Provisions	Suggested Audit Steps	Impact of Deficiency (To Be Included in Audit Comment)
3. Individuals should only work under their own passwords or other access keys and should not share these with others. Individuals should not log on to the system in order to provide another person access to the system.	1. Determine that an approved SOP or other formal policy/procedure exists to preclude the sharing of passwords and logging on to the system to allow someone else to access the system. 2. Confirm compliance with the control by reviewing documented evidence of compliance.	The risk of unauthorized access to the electronic data and to the computerized system is increased when there is a lack of an effective control (including documented evidence of compliance) to preclude sharing of passwords and logging on to the system to allow someone else to access the system.
4. Passwords or other access keys should be changed at established intervals.	1. Determine that an approved SOP or other formal policy/procedure exists that facilitates changing of passwords or other keys at established intervals. 2. Confirm compliance with the control by reviewing documented evidence of compliance.	The risk of unauthorized access to the electronic data and to the computerized system is increased when there is a lack of an effective control (including documented evidence of compliance) to facilitate changing of passwords or other keys at established intervals.
5. When someone leaves a workstation, the person should log off the system. Failing this, an automatic log off may be appropriate for long idle periods. For short periods of inactivity, there should be some kind of automatic protection against unauthorized data entry.	1. Determine that an approved SOP or other formal policy/procedure exists that facilitates automatic log off after a pre-determined period of time. 2. Confirm compliance with the control by reviewing documented evidence of compliance.	The risk of unauthorized access to the electronic data and to the computerized system is increased when there is a lack of an effective control (including documented evidence of compliance) to facilitate automatic log off after a pre-determined period of time.
B. Audit Trails		
1a. Persons must use secure, computer-generated, time-stamped audit trails to independently record the date and time of operator entries and actions that create, modify, or delete electronic records. A record is created when it is saved to durable media, as described under "commit" in Section II, Definitions.	1. Review the approved functional specifications to determine if the following requirement is included: a secure, computer-generated, time-stamped audit trail is independently generated to record the date and time of operator entries and actions that create, modify, or delete electronic records. 2. Review the approved technical specifications to determine if the following requirement is designed and programmed properly: a secure, computer-generated, time-stamped audit trail is independently generated to record the date and time of operator entries and actions that create, modify, or delete electronic records. 3. Review the test cases and scripts and document test results to confirm that a secure, computer-generated, time-stamped audit trail is independently generated to record the date and time of operator entries and actions that create, modify, or delete electronic records.	The lack of an effective audit trail limits the study sponsor's ability to (1) protect the authenticity, integrity, and, when appropriate, the confidentiality of electronic records and (2) reconstruct and evaluate study records.
1b. Audit trails must be retained for a period at least as long as that required for the subject electronic records ... and must be available for Agency review and copying.	1. Determine that an approved SOP or other formal record retention policy exists that mandates the retention of audit trails for a period at least as long as that required for the subject electronic records. 2. Confirm compliance with the SOP or other record retention policy by reviewing documented evidence of compliance. 3. Observe the audit trails (either hard copy or electronic) and confirm the existence and effectiveness of procedures designed to copy the audit trails.	As above.
2. Personnel who create, modify, or delete electronic records should not be able to modify the audit trails.	1. Review the security/authorization profiles to confirm that personnel who create, modify, or delete electronic records do not have written access to the audit trails. 2. Review the test cases and scripts and documented test results to confirm that testing verifies that personnel who create, modify, or delete electronic records cannot modify the audit trails.	Unauthorized access to audit trail records increases the risk that the audit trail data will be corrupted and therefore not usable to (1) protect the authenticity, integrity, and, when appropriate, the confidentiality of electronic records and (2) reconstruct and evaluate study records.

Figure 1

Continued

Guidance Document Provisions	Suggested Audit Steps	Impact of Deficiency (To Be Included in Audit Comment)
3. Clinical investigators should retain either the original or a certified copy of audit trails.	Perform a documentation review of the clinical investigators to confirm that they are in possession of either the original or a certified copy of audit trails. In the case of changes to the system, this also includes copies of source code and change control documentation, so the scope would also include developer and support personnel.	The original audit trails (or a certified copy) provide the documented evidence of study conduct. The lack of such documentation, and the ability to review the documentation, increases the risk that improper, incomplete, and/or inaccurate processing will go undetected.
4. FDA personnel should be able to read audit trails both at the study site and at any other location where associated electronic study records are maintained.	Observe the audit trails and all associated electronic study records (e.g., Case Record Forms [CRFs]), source code, change control documentation), in all locations where they are maintained, and confirm the existence and effectiveness of procedures designed to copy the audit trails.	The original audit trails (or a certified copy) provide the documented evidence of study conduct. The lack of such documentation, and the ability to review the documentation, increases the risk that improper, incomplete, and/or inaccurate processing will go undetected.
5. Audit trails should be created incrementally, in chronological order, and in a manner that does not allow new audit trail information to overwrite existing data in violation of §11.10(e).	1. Review the approved functional specifications to determine if the following requirement is included: audit trails should be created incrementally, in chronological order, and in a manner that does not allow new audit trail information to overwrite existing data. 2. Review the approved technical specifications to determine if the following requirement is designed and programmed properly: audit trails are created incrementally, in chronological order, and in a manner that does not allow new audit trail information to overwrite existing data. 3. Review the test cases and scripts and documented test results to confirm that audit trails are created incrementally, in chronological order, and in a manner that does not allow new audit trail information to overwrite existing data.	The lack of a complete audit trail increases the risk that improper, incomplete, and/or inaccurate processing will go undetected.
C. Date/Time Stamps		
The ability to change the date or time should be limited to authorized personnel and such personnel should be notified if a system date or time discrepancy is detected. Changes to date or time should be documented.	1. Review the security/authorization profiles to confirm that authorization to change the date or time is limited to system administration or other appropriate personnel. 2. Review the test cases and scripts and documented test results to confirm that testing confirms that only the authorized personnel can change the date or time. 3. Determine that an approved SOP or other formal policy/procedure(s) exists that facilitates (1) notification to the appropriate staff if a system date or time discrepancy is found and (2) that changes in date or time are documented. 4. Confirm compliance with the SOP or other record retention policies by reviewing documented evidence of compliance.	The lack of an effective control to ensure that the system's date and time are correct increases the risk that improper, incomplete and/or inaccurate processing will take place.
Dates and times are to be local to the activity being documented and should include the year, month, day, hour, and minute.	1. Review the approved functional specifications to determine if the following requirement is included: dates and times are to be local to the activity being documented and should include the year, month, day, hour, and minute. 2. Review the approved technical specifications to determine if the following requirement is designed and programmed properly: dates and times are local to the activity being documented and should include the year, month, day, hour, and minute. 3. Review the test cases and scripts and documented test results to confirm that dates and times are local to the activity being documented and should include the year, month, day, hour, and minute.	As above.

Figure 1
Continued

Guidance Document Provisions	Suggested Audit Steps	Impact of Deficiency (To Be Included in Audit Comment)
VI. SYSTEM FEATURES		
A. Facilitating the Collection of Quality Data		
Prompts, flags, or other help features within the computerized system should be used to encourage consistent use of clinical terminology and to alert the user to data that are out of acceptable range. Features that automatically enter data into a field when that field is bypassed should not be used.	1. Review the approved functional specifications to determine if the following requirements are included: (1) consistent use of clinical terminology; (2) alerts to the user regarding data that are out of acceptable range; (3) features that automatically enter data into a field when that field is bypassed and cannot be used. 2. Review the approved technical specifications to determine if the following requirement is designed and programmed properly: (1) consistent use of clinical terminology; (2) alerts to the user regarding data that are out of acceptable range; (3) features that automatically enter data into a field when that field is bypassed are not used. 3. Review the test cases and scripts and documented test results to confirm that (1) consistent use of clinical terminology is employed; (2) users are alerted when data are out of acceptable range; (3) features that automatically enter data into a field when that field is bypassed are not used.	The lack of an effective control to facilitate the collection of quality data increases the risk that improper, incomplete, inconsistent and/or inaccurate data will be collected. This, in turn, can increase the risk to the integrity of the data and decrease the efficiency of the study processing.
Electronic patient diaries and e-CRFs should be designed to allow users to make annotations... The record should clearly indicate who recorded the annotations and when (date and time).	1. If electronic diaries or e-CRFs are used, review the approved functional specifications to determine if the following requirements are included: (1) annotations are permitted; (2) the study record should clearly indicate who recorded the annotations and when (date and time). 2. Review the approved technical specifications to determine if the following requirement is designed and programmed properly: (1) annotations are permitted; (2) the study record clearly indicates who recorded the annotations and when (date and time). 3. Review the test cases and scripts and documented test results to confirm that (1) annotations are permitted; (2) the study record clearly indicates who recorded the annotations and when (date and time).	Annotations represent study data. The lack of an effective means to facilitate the collection of quality data increases the risk that improper, incomplete, and/or inaccurate data will be collected. This, in turn, can increase the risk to the integrity of the data.
B. Facilitating the Inspection and Review of Data		
Systems used for direct entry of data should be designed to include features that will facilitate the inspection and review of data. Data tags (e.g., different color, different font, flags) should be used to indicate which data have been changed or deleted, as documented in the audit trail.	1. If direct data entry is applicable, review the approved functional specifications to determine if the following requirement is included: features (e.g., data tags) to facilitate inspection and review. 2. Review the approved technical specifications to determine if the following requirement is designed and programmed properly: features (e.g., data tags) to facilitate inspection and review. 3. Review the test cases and scripts and documented test results to confirm that features (e.g., data tags) to facilitate inspection and review are operational.	The lack of an effective means to facilitate the collection of quality data increases the risk that improper, incomplete, inconsistent and/or inaccurate data will be collected. This, in turn, can increase the risk to the integrity of the data and decrease the efficiency of the study processing.
C. Retrieval of Data		
Recognizing that computer products may be discontinued or supplanted by newer (possibly incompatible) systems, it is nonetheless vital that sponsors retain the ability to retrieve and review the data recorded by the older systems. This may be achieved by maintaining support for the older systems or transcribing data to the newer systems.	1. Determine that an approved SOP or other formal policy/procedure exists that addresses maintenance/support of older systems and/or the transcribing of data to the newer systems. 2. Confirm compliance with the SOP or other policy by reviewing the older system documentation or the evidence of transcription. 3. Observe the audit trails (either hard copy or electronic) and confirm the existence and effectiveness of procedures designed to copy the audit trails. 4. For systems that are being, or will be, migrated,	FDA expects to be able to reconstruct a study, and expects that study sponsors be able to do so as well. This applies not only to the data, but also how the data were obtained or managed. The lack of complete information regarding versions of application software, operating systems, and software development tools, as well as applicable hardware, involved in the process-

Figure 1

Continued

Guidance Document Provisions	Suggested Audit Steps	Impact of Deficiency (To Be Included in Audit Comment)
When migrating to newer systems, it is important to generate accurate and complete copies of study data and collateral information relevant to data integrity. This information would include, for example, audit trails and computational methods used to derive the data. Any data retrieval software, script, or query logic used for the purpose of manipulating, querying, or extracting data for report generating purposes should be documented and maintained for the life of the report. The transcription process needs to be validated.	determine that a migration plan exists and that it addresses the following: generating accurate and complete copies of study data and collateral information relevant to data integrity; documenting and maintaining data retrieval software, script, or query logic used for the purpose of manipulating, querying, or extracting data for report generating purposes; validating the transcription process. 5. For systems that have been migrated, determine that the following objectives have been achieved: documented evidence exists to confirm that accurate and complete copies of study data and collateral information relevant to data integrity have been generated; data retrieval software, script, or query logic used for the purpose of manipulating, querying, or extracting data for report generating purposes is documented and is being maintained according to an approved SOP or other formal policy/procedure; the transcription process has been validated.	ing of data or records limits the Agency's ability to reconstruct and evaluate study records.
D. Reconstruction of Study		
...[A]ll versions of application software, operating systems, and software development tools involved in processing of data or records should be available as long as data or records associated with these versions are required to be retained.	1. Determine that an approved SOP or other formal policy/procedure exists that mandates the retention of all versions of application software, operating systems, and software development tools involved in processing of data or records for as long as data or records associated with these versions are required to be retained. 2. Confirm compliance with the SOP or other record retention policy by reviewing documented evidence of compliance.	FDA expects to be able to reconstruct a study. This applies not only to the data, but also how the data were obtained or managed. The lack of complete information regarding versions of application software, operating systems, and software development tools involved in processing data or records limits the Agency's ability to reconstruct and evaluate study records.
VII. SECURITY		
A. Physical Security		
Staff should be thoroughly aware of system security measures and the importance of limiting access to authorized personnel. *SOPs should be in place for handling and storing the system to prevent unauthorized access.*	1. Determine that approved SOPs or other formal policies/procedures exist that mandate (1) training for personnel who use the system and maintain/support the system on the applicable security policies and procedures and (2) for handling and storing the system to prevent unauthorized access. 2. Confirm compliance with the approved SOPs or other formal policies/procedures by reviewing documented evidence of compliance. With respect to training, this would include an inspection of the training records and evidence of staff understanding of the information learned (e.g., test results).	In addition to internal safeguards built into the system, external safeguards should be in place to ensure that access to the computerized system and to the data is restricted to authorized personnel. The lack of such safeguards increases the risk of unauthorized/improper processing. This is a limitation on data integrity.
B. Logical Security		
Access to the data at the clinical site should be restricted and monitored through the system's software with its required log-on, security procedures, and audit trail. The data should not be altered, browsed, queried, or reported via external software applications that do not enter through the protective system software.	1. Review the approved functional specifications to determine if the following requirements are included: (1) access to the data at the clinical site (e.g., investigator site, sponsor database) should be restricted and monitored through the system's software with its required log-on, security procedures, and audit trail; (2) the data should not be altered, browsed, queried, or reported via external software applications that do not enter through the protective system software. 2. Review the approved technical specifications to determine if the following requirements are designed and programmed properly: (1) access to the data at the clinical site (e.g., investigator site, sponsor database) is restricted and monitored through the system's software with its required	The risk of unauthorized access to the electronic data and to the computerized system is increased when there is a lack of effective logical security control (including documented evidence of compliance).

Figure 1

Continued

Guidance Document Provisions	Suggested Audit Steps	Impact of Deficiency (To Be Included in Audit Comment)
	log-on, security procedures, and audit trail; (2) the data is not to be altered, browsed, queried, or reported via external software applications that do not enter through the protective system software. 3. Review the test cases and scripts and documented test results to confirm: (1) access to the data at the clinical site (e.g., investigator site, sponsor database) is restricted and monitored through the system's software with its required log-on, security procedures, and audit trail; (2) the data cannot be altered, browsed, queried, or reported via external software applications that do not enter through the protective system software.	
There should be a cumulative record that indicates, for any point in time, the names of authorized personnel, their titles, and a description of their access privileges. The record should be in the study documentation accessible at the site.	1. Review the approved functional specifications to determine if the following requirements are included: a cumulative record should exist that indicates, for any point in time, the names of authorized personnel, their titles, and a description of their access privileges. 2. Review the approved technical specifications to determine if the following requirement is designed and programmed properly: a cumulative record is generated that indicates, for any point in time, the names of authorized personnel, their titles, and a description of their access privileges. 3. Review the test cases and scripts and documented test results to confirm: a cumulative record exists that indicates, for any point in time, the names of authorized personnel, their titles, and a description of their access privileges. 4. Perform a documentation review to confirm that the authorization records is available in the study documentation.	A cumulative record that indicates, for any point in time, the names of authorized personnel, their titles, and a description of their access privileges is an audit trail of authorization privileges. The lack of a complete audit trail increases the risk that improper, incomplete, and/or inaccurate processing will go undetected.
If a sponsor supplies computerized systems exclusively for clinical trials, the systems should remain dedicated to the purpose for which they were intended and validated.	1. Determine that approved SOPs or other formal policies/procedures exist that mandate a periodic review to ensure that the systems remain dedicated to the purpose for which they were intended and validated. 2. Confirm compliance with the approved SOPs or other formal policies/procedures by reviewing documented evidence of compliance. If undocumented/unvalidated changes to the system are identified, determine if documented justification exists for not documenting/validating the changes.	If the system is not completely dedicated to the purpose for which it was intended and validated, the ability to collect quality data is jeopardized. The lack of an effective means to facilitate the collection of quality data increases the risk that improper, incomplete, inconsistent, and/or inaccurate data will be collected. This, in turn, can increase the risk to the integrity of the data and decrease the efficiency of the study processing.
If a computerized system being used for the clinical study is part of a system normally used for other purposes, efforts should be made to ensure that the study software is logically and physically isolated as necessary to preclude unintended interaction with non-study software. If any of the software programs are changed the system should be evaluated to determine the effect of the changes on logical security.	1. Review the approved technical specifications to determine if the system is part of a system normally used for other purposes and, if so, the specification includes details of how the study software is logically and physically isolated as necessary to preclude unintended interaction with non-study software. 2. Review the test cases and scripts and documented test results to confirm that study software is logically and physically isolated from non-study software. 3. Determine that approved SOPs or other formal policies/procedures exist that mandate that changes to software programs are evaluated to determine the effect of the changes on logical security. 4. Confirm compliance with the approved SOPs or other formal policies/procedures by reviewing documented evidence of compliance.	As above.
Controls should be in place to prevent, detect, and mitigate effects of computer viruses on study data and software.	1. Determine that approved SOPs or other formal policies/procedures exist that mandate precautions against computer viruses and training for	A computer virus represents an attempt to access records in an unauthorized manner. Unauthorized access to study records increases

Figure 1

Continued

Guidance Document Provisions	Suggested Audit Steps	Impact of Deficiency (To Be Included in Audit Comment)
	staff in these precautions. 2. Confirm compliance with the approved SOPs or other formal policies/procedures by reviewing documented evidence of compliance. With respect to training, this would include an inspection of the training records and evidence of staff understanding of the information learned (e.g., test results). 3. Determine that an appropriate anti-virus software package is employed to detect viruses and confirm that procedures are in place to confirm its effectiveness.	the risk that such records will be corrupted and therefore not usable to (1) protect the authenticity, integrity, and, when appropriate, the confidentiality of electronic records and (2) reconstruct and evaluate study records.
VIII. SYSTEM DEPENDABILITY		
The sponsor should ensure and document that computerized systems conform to the sponsor's established requirements for completeness, accuracy, reliability, and consistent intended performance.	Perform a documentation review at each applicable site at which the system is developed, operated and/or supported to determine the existence of current approved functional specifications, approved technical specifications, operations manuals, pertinent approved SOPs and other procedures, and applicable reference documentation.	Systems documentation provides information that describes what the software is intended to do and how it is intended to do it. The lack of such documentation limits management's ability to effectively manage the study and the Agency's ability to reconstruct and evaluate study records.
A. Systems Documentation		
Systems documentation should be readily available at the site where clinical trials are conducted. Such documentation should provide an overall description of computerized systems and the relationship of hardware, software, and physical environment.		
B. Software Validation		
FDA may inspect documentation, possessed by a regulated company, that demonstrates validation of software.	1. Determine that approved SOPs or other formal policies/procedures exist that provide the requirements for system validation, as defined in the guidance document, and the requirement to ensure that the documentation can be inspected by FDA. 2. Confirm compliance with the approved SOPs or other formal policies/procedures by reviewing documented evidence of compliance. This would involve reviewing the validation documentation for each applicable system to ensure that all validation deliverables are provided in the validation file.	Validation documentation represents documented evidence that the system operates as intended and will continue to do so. The lack of such documentation, or the lack of FDA's ability to review such documentation, limits the Agency's ability to reconstruct and evaluate study records.
1. For software purchased off-the-shelf, most of the validation should have been done by the company that wrote the software. The sponsor or contract research organization should have documentation (either original validation documents or on-site vendor audit documents) of this design-level validation by the vendor, and should have itself performed functional testing (e.g., by use of test data sets) and researched known software limitations, problems, and defect corrections.	1. Determine that approved SOPs or other formal policies/procedures exist that mandates: (1) the performance of a vendor audit when necessary to assess the effectiveness of the design level validation by the vendor; (2) the performance of an adequate level of functional testing based upon the effectiveness of the vendor's validation status; (3) researching known software limitations, problems, and defect corrections. 2. Confirm compliance with the approved SOPs or other formal policies/procedures by reviewing documented evidence of compliance. This would include a formal audit report documenting the results of the vendor audit.	The sponsor's ability to ensure and document that computerized systems conform to the sponsor's established requirements for completeness, accuracy, reliability, and consistent intended performance will be limited without a vendor audit, adequate functional testing, knowledge of software limitations, problems, and defect corrections.
In the special case of database and spreadsheet software that is (1) purchased off-the-shelf, (2) designed for and widely used for general purposes, (3) unmodified, and (4) not being used for direct entry of data, the sponsor or contract research organization may not have documentation of design level validation. However, the sponsor or contract research organization should have itself performed functional testing (e.g., by use of test data sets) and researched known software limitations, problems, and defect corrections.	1. Determine that approved SOPs or other formal policies/procedures exist that mandates, in the case where design level validation is unavailable, performing an adequate level of functional testing based upon the effectiveness of the vendor's validation status and researching known software limitations, problems, and defect corrections. 2. Confirm compliance with the approved SOPs or other formal policies/procedures by reviewing documented evidence of compliance.	The sponsor's ability to ensure and document that computerized systems conform to the sponsor's established requirements for completeness, accuracy, reliability, and consistent intended performance will be limited without adequate functional testing and knowledge of software limitations, problems, and defect corrections.

Figure 1
Continued

Guidance Document Provisions	Suggested Audit Steps	Impact of Deficiency (To Be Included in Audit Comment)
2. Documentation important to demonstrate software validation includes: *Written design specification that describes what the software is intended to do and how it is intended to do it;* *A written test plan based on the design specification, including both structural and functional analysis; and* *Test results and an evaluation of how these results demonstrate that the predetermined design specification has been met.*	1. Determine that approved SOPs or other formal policies/procedures exist that provide the requirements for system validation, as defined in this section of the guidance document, and the requirement to ensure that the documentation can be inspected by FDA. 2. Confirm compliance with the approved SOPs or other formal policies/procedures by reviewing documented evidence of compliance. This would involve reviewing the validation documentation for each applicable system to ensure that all validation deliverables are provided in the validation file.	Validation documentation represents documented evidence that the system operates as intended and will continue to do so. The lack of such documentation, or the lack of FDA's ability to review such documentation, limits the Agency's ability to reconstruct and evaluate study records.
C. Change Control		
Written procedures should be in place to ensure that changes to the computerized system such as software upgrades, equipment or component replacement, or new instrumentation will maintain the integrity of the data or the integrity of protocols. *The impact of any change to the system should be evaluated and a decision made regarding the need to revalidate. Revalidation should be performed for changes that exceed operational limits or design specifications.* *All changes to the system should be documented.*	1. Determine that approved SOPs or other formal policies/procedures exist that provide a formal change control procedure designed to ensure that changes to the computerized system such as software upgrades, equipment, component replacement, or new instrumentation will maintain the integrity of the data or the integrity of protocols. The SOPs or other procedures should include an evaluation of the impact of changes to determine if revalidation is required. 2. Confirm compliance with the approved SOPs or other formal policies/procedures by reviewing documented evidence of compliance. If undocumented/unvalidated changes to the system are identified, determine if documented justification exists for not documenting/validating the changes.	Change control procedures represent an audit trail of changes to the automated processes. The lack of a complete audit trail, including changes to associated documentation, increases the risk that improper, incomplete, and/or inaccurate processing will go undetected.
IX. SYSTEM CONTROLS		
A. Software Version Control		
Measures should be in place to ensure that versions of software used to generate, collect, maintain, and transmit data are the versions that are stated in the systems documentation.	1. Determine that approved SOPs or other formal policies/procedures exist that provide configuration control requirements; that is, controls to ensure that all elements of the system configuration (e.g., hardware, software, documentation) remain consistent throughout the life of the system. 2. Confirm compliance with the approved SOPs or other formal policies/procedures by reviewing documented evidence of compliance.	Change control procedures represent an audit trail of changes to the automated processes. Version control represents an identification of the different components resulting from the change. The lack of a complete audit trail, including controls over identifying the various versions, increases the risk that improper, incomplete, and/or inaccurate processing will go undetected.
B. Contingency Plans		
Written procedures should describe contingency plans for continuing the study by alternate means in the event of failure of the computerized system.	1. Determine that an approved contingency plan (a.k.a., disaster recovery plan) exists that describes plans for continuing the study by alternate means in the event of failure of the computerized system or inability to access the system or facility. 2. Confirm that the disaster recovery plan was completely tested and that the test results are documented.	The lack of a contingency plan increases the risk of not being able to collect data in the event of failure of the computerized system or inability to access the system or facility. The lack of an effective means to facilitate the collection of quality data increases the risk that improper, incomplete, inconsistent and/or inaccurate data will be collected. This, in turn, can increase the risk to the integrity of the data and decrease the efficiency of the study processing.
C. Backup and Recovery of Electronic Records		
Backup and recovery procedures should be clearly outlined in the SOPs and be sufficient to protect against data loss.	1. Determine that approved SOPs or other formal policies/procedures exist that mandate periodic backup of programs and files, storage of backup programs and files in a secure location, and applicable recovery procedures (including the mainte-	Records should be backed up regularly in a way that would prevent a catastrophic loss and ensure the quality and integrity of the data.

Figure 1

Continued

Guidance Document Provisions	Suggested Audit Steps	Impact of Deficiency (To Be Included in Audit Comment)
Backup records should be stored at a secure location specified in the SOPs. *Backup and recovery logs should be maintained to facilitate an assessment of the nature and scope of data loss resulting from a system failure.*	nance of recovery logs). 2. Confirm compliance with the approved SOPs or other formal policies/procedures by reviewing documented evidence of compliance. This would include an audit of the backup site to confirm the completeness and accuracy of the inventory therein.	
X. TRAINING OF PERSONNEL		
A. Qualifications		
Each person who enters or processes data should have the education, training, and experience or any combination thereof necessary to perform the assigned functions. *Individuals responsible for monitoring the trial should have education, training, and experience in the use of the computerized system necessary to adequately monitor the trial.*	1. Determine that approved SOPs or other formal policies/procedures exist that mandate that each person who enters or processes data, persons who monitors the trial, and persons who conduct the training, should have the education, training, and experience or any combination thereof necessary to perform the assigned functions. 2. Confirm compliance with the approved SOPs or other formal policies/procedures by reviewing documented evidence of compliance. With respect to training, this would include an inspection of the training records and evidence of staff understanding of the information learned (e.g., test results).	Lack of education, training, and experience to perform study-related activities, and documented evidence thereof, increases the risk that improper, incomplete, inconsistent and/or inaccurate data will be collected. This, in turn, can increase the risk of the integrity of the data and decrease the efficiency of the study processing.
B. Training		
Training should be provided to individuals in the specific operations that they are to perform. *Training should be conducted by qualified individuals on a continuing basis, as needed, to ensure familiarity with the computerized system and with any changes to the system during the course of the study.*	As above.	As above.
C. Documentation		
Employee education, training, and experience should be documented.	1. Determine that records of education, training, and experience exist. 2. Perform a review of these records and confirm that they are current.	As above.
XI. RECORDS INSPECTION		
A. ...[S]ystems should be able to generate accurate and complete copies of records in both human readable and electronic form suitable for inspection, review, and copying by the Agency.	1. Determine that approved SOPs or other formal policies/procedures exist that mandate that systems should be able to generate accurate and complete copies of records in both human readable and electronic form suitable for inspection, review, and copying. 2. Confirm compliance with the approved SOPs or other formal policies/procedures by reviewing documented evidence of compliance. For a given system, this would include testing and documented test results to confirm this functionality.	FDA may inspect all records that are intended to support submissions to the Agency, regardless of how they were created or maintained. The lack of appropriate documentation, lack of FDA's ability to review such documentation, and/or lack of applicable hardware and software to perform required processes limits the Agency's ability to reconstruct and evaluate study records.
B. The sponsor should be able to provide hardware and software as necessary for FDA personnel to inspect the electronic documents and audit trail at the site where an FDA inspection is taking place.	Perform a documentation review at the applicable site(s) to determine the existence of the hardware and software specified in the approved technical specification.	FDA may inspect all records that are intended to support submissions to the Agency, regardless of how they were created or maintained. The lack of appropriate documentation, lack of FDA's ability to review such documentation, and/or lack of applicable hardware and software to perform required processes limits the Agency's ability to reconstruct and evaluate study records.

Figure 1
Continued

Guidance Document Provisions	Suggested Audit Steps	Impact of Deficiency (To Be Included in Audit Comment)
XII. CERTIFICATION OF ELECTRONIC SIGNATURES		
As required by 21 CFR 11.100(c), persons using electronic signatures to meet an FDA signature requirement shall, prior to or at the time of such use, certify to the agency that the electronic signatures in their system, used on or after August 20, 1997, are intended to be the legally binding equivalent of traditional handwritten signatures.	If electronic signatures are being used to meet an FDA signature requirement, determine that the certification was filed as specified in 21 CFR Part 11.	This certification is a legal document created by persons to acknowledge that their electronic signatures have the same legal significance as their traditional handwritten signatures. The lack of such certification means that the electronic signatures will not be the legally binding equivalent of traditional handwritten signatures.

Audit Checklist

The internal auditor should develop an audit checklist using the contents of *Figure 1* to facilitate collecting and evaluating information. While the author suggests organizing the checklist to correspond to the guidance document provisions, the internal auditor can use whatever organization makes the most sense. The key issue is to ensure that all guidance document provisions are addressed.

Summary

This is the place to start if you are, or are thinking about, performing an audit for electronic records compliance. Remember, the internal audit is a tool to advise management as to compliance with the 21 CFR Part 11 regulation. You need to be both thorough and efficient. This article provides the means to achieve both objectives. ❑

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Software Supplier Assessment Plan

The life cycle for software parallels that for a computer system. It begins during the analysis of the requirements...

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It has long been recognized that two of the most critical steps in the development life cycle of a computer system are the definition of the system's functional requirements and the development of high quality software. Regarding quality, FDA stated in the *Federal Register* (Volume 61, Number 87, May 3, 1996) covering proposed changes to 21 CFR Parts 210 and 211 that "The GMP regulations are based on fundamental concepts of quality assurance: (1) Quality, safety, and effectiveness must be designed and built into a product; (2) quality cannot be inspected or tested into a finished product; and (3) each step of the manufacturing process must be controlled to maximize the likelihood that the finished product will be acceptable." These basic quality principles are directly applicable to the development and validation of computer systems, and associated software for GXP (i.e., GLP, GMP, and GCP) applications in the pharmaceutical and health care industry.

Background

The life cycle for software parallels that for a computer system. It begins during the analysis of the requirements for the system and proceeds throughout all stages of the system development life cycle until the system is retired. The quality of a computer system must be built in during creation of the software. To assure that important aspects of quality are met, it is important for the software user to obtain assurance that the supplier has followed the appropriate software development and configuration management practices. The assessment should establish the following:

- Written development standards and procedures are being followed;
- Test plans and test methods adequately demonstrate that the software meets requirements;
- Good configuration management and documentation practices are utilized.

Assessments of potential software suppliers should be made by the end-user prior to selection of the supplier. Once a supplier is selected, additional performance reviews should be conducted throughout the course of the project.

Since the elements of an assessment and the requirements for documentation of the development process are heav-

ily dependent on the type of software being developed, it would be appropriate at this point to define those classifications. Software can be classified into system, configurable and application-specific software. These classifications are not considered to be rigid or mutually exclusive, but they allow important distinctions to be made about vendor-supplied software and software testing. Operating system software provides basic operating instructions for the computer. Examples of system software include DOS and UNIX. Since operating system software (which is supplied with the computer) has a very large user base and is independent of the specific application, it does not require formal validation. Configurable software is a program which allows the user to define a number of conditions such as operating parameters, reporting parameters and alarm conditions. The user does not change the configurable program code itself, but can change the parameters to satisfy the requirements of a specific application. Lotus 1-2-3 and most Distributed Control System (DCS) software are examples of configurable software. Validation of configurable software is heavily dependent on assessing a supplier's practices, and the quality of documentation generated during software development and testing.

Application-specific software is code which is written to the specific requirements of the end-user in their application.

Application-specific software is code which is written to the specific requirements of the end-user in their application. When a configurable program is used, the parameters and operations which are specified via the configurable software comprise the application-specific program. Examples would include designing a spread sheet in Lotus 1-2-3 to calculate yield of a particular mixing operation or setting up a Microsoft ACCESS database to track product complaints. (Note: If the program code of configurable software is altered for a specific end-user's application, the entire code is considered to be application-specific software.) Since application-specific software directly controls the functionality of a computerized system, it requires the greatest degree of validation documentation. The documentation for both application-specific and configurable software are often scrutinized by the FDA during an inspection, since both have the potential for adversely affecting the operation of the computer-related system.

In the case of vendor-supplied software (both configurable and application-specific software), the end-user assumes the ultimate responsibility for the use of the software. Thus, the user must rely heavily on vendor-supplied information and test data to assess the quality of their software. As part of an assessment, the user should carefully scrutinize the development and testing practices of the software developer to ensure that the software developer meets the appropriate standards. The quality assurance discipline of the end-user firm (or their representative) should be familiar enough with software development and testing practices to effectively participate in the performance of the assessment. As part of the assessment, the end-user should assess the software programmer's application of software quality assurance standards, guidelines, and standard operating procedures relative to software development, verification, validation, and maintenance. Detailed studies of this documentation, as well as test cases, test reports, software anomaly and/or bug fix reports and change reports establish the integrity and worth of the software developer's product. Related factors to consider as part of an assessment are the software supplier's use of written quality assurance, testing and configuration management procedures, the experience level of their programmers, and the quality and depth of their documentation. For configurable software, the user base for the specific version of the configurable program being used, length of vendor support for prior versions, and their financial stability are also important considerations.

An important part of the software development life cycle for both configurable and application-specific software, is how it is tested and documented. Thorough documentation is imperative throughout all stages of software development, including: requirements, design, programming, and testing. While demonstrating compliance with requirements and development standards, testing also shows

functionality, compatibility, and performance. Most important, testing identifies non-conformance with end-user requirements and accepted software development practices.

Software testing is classified as structural or functional testing. Experience has shown that structural testing, and the detailed examination of the functional logic of code, may be the most important step in building quality into software. Structural testing includes peer review of the code to determine if it meets user requirements/specifications and structurally adheres to established standards/procedures. Structural testing also includes analysis of all logic paths, and inspection for "dead" code. Dead code is executable code that is extraneous to the normal operation of the system. On board diagnostics, utilities, configurable code, in-line code comments or other compiled code that is not accessed on a regular basis is not considered dead code.

A listing of the source code (the human readable form of the code) must be available to perform structural testing. In its 1986 concept paper, PhRMA's (formerly PMA's) Computer Systems Validation Committee (CSVC) advised that source code for application-specific software should generally be available to the end-user. (In the same concept paper the CSVC also emphasized the importance of having written procedures that are followed when preparing or altering any software.) FDA Policy Guide 7132a.15 published in May, 1987, emphasized three key points regarding source code:

- User-firms should maintain source code for vendor-supplied application programs.
- User-firms should review and approve such source codes.
- Dead code should be removed on the basis of such reviews.

Documentation of the structural testing of configurable and application-specific software is the software developer's responsibility, but the responsibility for determining the adequacy of this structural testing documentation lies with the end-user. Therefore, a decision to purchase supplier software should be dependent upon their ability to provide appropriate documentation of the structural integrity of their software. A supplier assessment should be performed if there are any concerns about the adequacy of their documentation, or whether or not the supplier developed the software using software development standards and/or procedures.

Functional testing of software evaluates the inputs or range of inputs compared to the expected output values. Functional testing does not require source code, but the source code can be helpful in designing tests to be performed. Functional testing does, however, require a comprehensive system specification that describes all functions of the platform in sufficient detail to define the tests required to assure proper performance. The supplier of configurable software may provide documented verification of functional testing of their software, but the end-user must also perform sufficient functional testing as part of operational qualification to verify the proper operation of the configurable software for their unique application and within their specific environment. Functional testing of application-specific software is generally the end-user's total responsibility. End-users who rely on vendors to perform functional testing of application-specific software need to obtain assurance of the vendor's education, training, computer validation experience and the adequacy of the testing documentation.

Assessment Matrix

An assessment matrix was developed by the authors to facilitate the performance and documentation of a supplier assessment, and to maintain consistency amongst the assessments performed. It is important to note that the matrix has aspects of both an assessment and an audit. An audit requires a pre-approved audit plan. An audit has a narrower, defined scope, and examines documentation in terms of compliance with traceable directives such as applicable regulatory requirements, standard operating procedures, accepted standards, manufacturing procedures, project and quality assurance plans, etc. The audit report includes observations for documents, and conclusions relative to the software developer's performance and compliance with appropriate directives. An assessment on the other hand is informal, has a much broader scope, and examines documentation in terms of current industry practice and regulatory agency expectations. An assessment report is subsequently generated that offers an opinion based on experience in the industry as to the level of compliance of reviewed documentation, and offers suggestions for improvement.

Many of the items for review listed in the matrix

are directly traceable, and therefore referenced, to ISO 9000, viz., ISO 9001, Quality Systems – Model for Quality Assurance in Design/Development, Production, Installation and Servicing, and ISO 9000-3, Part 3, Guidelines for the Application of ISO 9001 to the Development, Supply and Maintenance of Software. FDA made the following statement regarding the ISO 9000 series of standards in the May 3, 1996 *Federal Register* cited above:

"Other organizations have developed standards to define quality in the manufacturing process. One such organization is the International Organization of Standardization (ISO). The purpose of the ISO 9000 Standards is to provide generic guidance on quality in manufacturing processes to both industry and vendors supplying industry. Five standards (9000-9004) have been developed by the ISO Council and are intended to be accepted worldwide. These standards are applicable to any industry and are not specific to the pharmaceutical industry. Compliance with the standards is voluntary. The principles and practices elucidated in the ISO standards are not in conflict with those provided by the cGMP regulations. Indeed, voluntary ISO standards share common principles with FDA's CGMP requirements."

A key word, used twice, in the above statement is 'voluntary'. It is because of the voluntary nature of the ISO Standards that they are not, and never will be, accepted by FDA as a substitute for GXP regulations. However, if one can provide a high level of assurance through a supplier assessment that ISO and/or ANSI/IEEE (also used in developing the assessment matrix) standards have indeed been followed in the development of whatever product and/or service the supplier is providing, our experience has shown that you will have demonstrated to FDA's satisfaction that the product/service is validatable.

A listing of the source code (the human readable form of the code) must be available to perform structural testing.

The rating/scoring system used in the performance of the assessment is as follows: a rating of Satisfactory (S) is equal to a score of 5, Needs Improvement (NI) is equal to a score of 3, and Needs Substantial Improvement (NSI) is a zero score. The highest total score attainable is 320. No attempt has been made to prioritize the importance of the items listed in the matrix since their importance is dependent on specific project requirements, i.e., the ranking would be dependent upon the reviewer's end use of the product/service. Thus, the ranking of the items should occur, if at all, after the assessment has been completed, when items with 'NSI' or 'NI' ratings can be prioritized relative to their potential impact on the validatability of the application.

Example Application and Assessment Findings

The following is an actual example of the application of the Assessment Matrix in the performance of an assessment of a software supplier. The company assessed, noted as "[CLIENT]," developed both configurable and application-specific software for their manufactured systems. At the time of the assessment [CLIENT] was developing new configurable software following a quality program that had been in place for less than a year.

The Corporate Quality Manual and other documentation related to the software development and validation process at [CLIENT] were evaluated using the Matrix described above. [CLIENT] scored 227 out of 320 points, leaving an improvement potential of 93. This was a very good rating considering the youth of [CLIENT's] quality program, and relative to similar assessments that have been performed using this approach. It is important to bear in mind that the observations and ratings summarized in the following completed matrix concerning the [CLIENT's] Corporate Quality Program pertain to the development and release of software and documentation solely. No evaluation of quality systems as they pertain to the manufacturing facilities was made as a part of this assessment plan matrix. The findings of the assessment too lengthy for inclusion in the comments section of the matrix are presented following the matrix. Recommendations for improvement for [CLIENT] are presented in Example Assessment Recommendations section.

Figure 1

Software Supplier Assessment Plan

No. Item	Reference	Rating	Score	Comment
1. Does the company have a formal quality policy?	ISO 9000-3-4.1.1.1	S	5	None
2. Does the company have an effective methodology to ensure understanding of the plan at all levels of the company?	ISO 9000-3-4.1.1.1	NI	3	See discussion below
3. Has the company assigned an individual or individuals to ensure the quality of work?	ISO 9000-3-4.1.1.2.1	S	5	None
4. Has the company assigned personnel and resources to the verification and validation activities independent from the code development process?	ISO 9000-3.4.1.1.2	NI	3	See discussion below
5. Has the company a means of advising management that the requirements of the quality plan are implemented and maintained?	ISO 9000-3 4.1.1.2.3	NSI	0	See discussion below
6. Does the company have a policy of conducting joint reviews between supplier and purchaser?	ISO 9000-3 4.1.3	NI	3	See discussion below
7. Does the company have a policy of establishing a unique quality plan for each project?	ISO 900-3 4.2.3	S	5	None
8. Does the company have a procedure for conducting internal audits to ensure compliance with the quality plan and adherence to standards?	ISO 9000-3 4.3	NSI	0	No procedure was available for review
9. If yes to Item 8, is there a policy that effectively notifies management of quality discrepancies?	ISO 9000-3 4.3	NSI	0	See Item 8 and discussions regarding the lack of formal management endorsement
10. Has the company written procedures to address the following issues:				
a. Investigating the causes of non-conforming product and corrective action necessary to prevent recurrence?		S	5	None
b. Analyzing all processes, work operations, concessions, quality records and customer complaints to detect and eliminate potential causes of non-conformance?		S	5	None
c. Initiating preventative actions to deal with problems corresponding to the risks encountered?		NI	3	The required actions should be formalized via a procedure
d. Applying controls to ensure that corrective actions are taken and that they are effective?		NI	3	Refer to item 10c
e. Implementing and recording changes in procedures resulting from corrective action?		NI	3	Refer to item 10c
11. Does the company have a policy in place to handle changes in the Purchasers requirements during development?	ISO 9000-3 5.2.2	NI	3	Item is addressed informally, but no procedure was available for review

Figure 1 (continued)

No. Item	Reference	Rating	Score	Comment
12. Does the company utilize a formal project development plan which covers the following issues:	ISO 9000-3 5.4.1			
a. The definition of the project, including a statement of its objectives, and with reference to related purchaser or supplier projects?		S	5	None
b. The organization of the project resources, including the team structure responsibilities, use of sub-contractors and material resources to be used?		S	5	None
c. Are development phases identified?		S	5	None
d. Are the individual plans, such as project quality plan, configuration management plan, integration plan and/or test plan identified?		NI	3	This area needs improvement even though it is addressed in several documents
13. Are the following phases formally identified and documented in the project development plan:	ISO 9000-3 5.4.2			
a. Development phases to be carried out?		NI	3	The policy covering this item is very recent with no history to review
b. Required inputs for each phase?		NI	3	See Item 13a
c. Required outputs (deliverables) for each phase?		NI	3	See Item 13a
d. Verification procedures to be carried out for each phase?		S	5	None
e. Analysis of potential problems associated with the development phases and with the achievement of specified requirements?		NI	3	See Item 13a
14. Does the company have a formal development plan that includes the following issues:	ISO 9000-3 5.4.2.2			
a. A schedule of development, implementation and associated deliverables?		NI	3	Issues addressed informally. Procedure needs to be formalized
b. A progress control mechanism?		NI	3	See Item 14a
c. A listing of organizational responsibilities, resource and work assignments?		NI	3	See Item 14a
d. A listing of organizational and technical interfaces between different groups, specifically between the software development effort and testing group?		S	5	None
15. Does the development plan identify methods for ensuring that all activities are carried out correctly and include:				
a. Rules, practices and conventions for software development?		S	5	None
b. Tools and techniques for development?		S	5	None
c. A configuration management plan?		NI	3	Item presently addressed informally. Procedure should be implemented

Figure 1 (continued)

No. Item	Reference	Rating	Score	Comment
16. Are progress meetings planned, held and documented to ensure that understanding resource issues are resolved and to ensure effective execution of the development plan?	ISO 9000-3 5.4.5	NI	3	None
17. Does the company have a policy to evaluate outputs from the development plan and, if so, is it documented?	ISO 9000-3 5.4.5	S	5	None
18. Does the company have a program that documents the outputs from each development phase and verifies the following issues:	ISO 9000-3 5.4.5			
a. That the outputs meets the relevant requirements?		S	5	None
b. Contains or references acceptance criteria for forwarding to subsequent phases?		S	5	None
c. Conforms to appropriate developmental practices and conventions?		S	5	None
d. Identifies those characteristics of the product that are critical to the product's safe and proper functioning?		S	5	None
19. Does the company have a procedure for the verification of all development phase outputs at the end of each phase?	ISO 9000-3	S	5	None
20. Does the development verification establish that the development phase outputs meet the corresponding input requirements by means of development control measures such as:				
a. Holding peer group development reviews at appropriate points in the development process?		S	5	None
b. Is a new design evaluated with proven similar design?		S	5	None
c. Are tests or demonstrations recorded or documented?		S	5	None
d. Are only verified development outputs submitted to configuration management and accepted for use in subsequent phases?		NI	3	Once again, while these actions occur, a formalized system should be implemented
21. Does the company prepare a project quality plan? If so does it meet the following criteria:				
a. States quality objectives, expressed in measurable terms?		NSI	0	A system needs to be implemented in this regard
b. Defines inputs and outputs for each development phase?		NSI	0	See Item 21a
c. Identifies the types of test, verification and validation issues for each phase of the project?		NSI	0	See Item 21a
22. Does the quality plan detail planning of testing, verification and validation activities, including schedules, resources and approval authorities?		NI	3	Portions of these areas are addressed, but a formal program should be implemented especially regarding approval authorities

Figure 1 (continued)

No. Item	Reference	Rating	Score	Comment
23. Does the quality plan detail specific responsibilities for quality activities such as:				
a.Reviews and testing?		S	5	None
b.Configuration management?		S	5	None
c.Defect control and corrective action?		NSI	0	Program needs to be implemented
24. Does the company routinely conduct Peer Group Code and Document Reviews?	ISO 9000-3 5.6.4	S	5	None
25. Is progress to the next phase prevented until the consequences of all identified deficiencies are satisfactorily resolved or the risk of proceeding otherwise is known?	ISO 9000-3 5.6.4	NI	3	Issues are addressed informally, but a formal program should be implemented
26. Does the company establish and review test plans, specifications and procedures prior to starting testing activities?	ISO 9000-3 5.7.2	NI	3	Issues are addressed informally but not described in a formal procedure
27. Has the company a written policy for:	ISO 9000-3 5.7.2			
a. Software unit, integration, system and acceptance testing?		NI	3	Methodology needs to be described in a formal procedure
b. Establishing test cases, test data and expected results?		S	5	None
c. The types of tests to be performed, e.g., functional tests, structural tests, boundary tests, and performance testing?		NI	3	See Item 27a
d. Identifying test environments, tools and test software?		S	5	None
e. Establishing acceptance criteria for test data?		S	5	None
f. Have required testing personnel and training been identified?		NI	3	See Item 27a
28. Does the company record test results and evaluate them as defined in the relevant specification?	ISO 9000-3 5.7.3	NI	3	None
a. Are discovered problems and their possible impact on other parts of the software tracked and are those responsible notified so that total problem resolution can be tracked until resolution is complete?		NI	3	A more formal system should be implemented and procedures regarding these items
b. Is test relevancy and adequacy evaluated?		NI	3	See Item 28a
c. Is hardware and software configuration considered and documented?		NI	3	See Item 28a
29. Is the product validated prior to delivery and acceptance by the purchaser to ensure a complete product under conditions similar to the application environment as specified in the contract?	ISO 9000-3 5.7.4	S	5	None
30. What actions drive a version up grade of software?	ISO 9000-3 5.9.1	NI	3	A more formal system should be implemented through a procedure that describes what an upgrade consists of and when an upgrade is to be issued
	TOTAL SCORE:		**227**	

An Assessment Report incorporating the above matrix was prepared that discussed the results of the on-site assessment. The report described the observations made during the review, and provided suggested approaches to correcting observed deficiencies and making the software development and validation process for computer-related systems more efficient and cost effective. The report also discussed general requirements for documentation of the packaged/skid-mounted computer/software systems manufactured by [CLIENT]. Findings of the assessment not included in the matrix are summarized below:

■ A review of the Corporate Quality Manual indicates a program that can be referenced to ISO 9000 with the following exceptions:

ISO 9001 stipulates that all quality issues shall be reported to executive management and executive endorsement of the plan shall be made. No statement of executive endorsement has been made in this manual. The principal issue in this regard is the establishment of the so-called Juran Triangle which calls for communication from management to the production function, to quality assurance and back to management. Frequently, this endorsement is made by the Chief Executive Officer of the corporation, the Board of Directors, or both. Plans without this endorsement have traditionally been found to be unenforceable as the adequate flow of appropriate data cannot be established. This omission has a substantial effect on many of the ratings given in the quality matrix.

Other findings omitted from the assessment plan matrix are:

■ Does the company have an effective methodology to ensure understanding of the plan at all levels of the company? – This item was rated NI as a result of the age of the program. There remains much to be accomplished in this regard due to the relative youth of the program. However, the company is relatively small, so this issue should not have a substantial effect on their quality program.

■ Has the company assigned personnel and resources to the verification and validation activities independent from the code development process? – As very little code has been developed in-house, this is not a significant concern at the present time. This issue was rated NI, as it is probable that the code development process will increase in the future, and a policy should be placed into effect that would preclude the software developer from testing their own code.

■ Has the company a means of advising management that the requirements of the quality plan are implemented and maintained? – Refer to the previous discussion on the lack of formal endorsement by executive management and its effect on the Juran Triangle. Without this endorsement, it cannot be demonstrated that this issue is properly addressed. This item was rated NSI.

■ Does the company have a policy of conducting joint reviews between supplier and purchaser? While it is readily apparent that [CLIENT] works very closely with their clients, this issue is one of the major tenants of ISO 9001. A formal policy outlying the conduct, frequency and content of these meetings should be implemented. This issue was rated NI.

Example Assessment Recommendations

The following recommendations were made in the Assessment Report:

It was determined from the assessment that many of the essential parts of a good program for software development and validation of computer-related systems were already in place. Some "gaps" in the content of reviewed documentation, and deficiencies in organization and administration of the software development and validation processes were observed in the assessment. However, considering the youth of [CLIENT's] quality program their progress was commendable. The highest score attainable using the assessment matrix is 320. [CLIENT] scored 227 (~3.5/Item), which is well above the average found in evaluating similar quality programs for the development and release of software and documentation, leaving an improvement potential of 93. Also noted during the course of our Assessment was [CLIENT's] commitment to improving the software development and validation processes for, and the quality of, their manufactured systems.

With regard to recommended improvements in [CLIENT's] quality program, Standard Operating Procedures (SOPs) covering certain aspects of development and maintenance of computer/software systems (e.g., generation of development documentation, testing methods, peer reviews,

backup and recovery, configuration management, business continuity, security, and evaluation of third-party vendors) were observed to be absent, or in need of revision to improve efficiency in administration.

It should be kept in mind in developing and refining a software development and validation program for computer-related systems, application-specific software (software developed to a client's specific requirements) is defined by FDA to be the same as master production and control records. In the background section of FDA Policy Guide 7132a.15 it is stated "In the case of computerized drug process control, certain information required by GMP to be in a master production record is contained in the source code for the application program... Because the source code ultimately has a direct and significant bearing on drug product quality as manual batch records, it is vital that source code and supporting documentation be reviewed and approved by the drug manufacturer prior to implementation, and be maintained as the GMP require for master production and control records. (e.g., see 21 CFR 211.100, 211.180, and 211.186.) Careful review of source code and its documentation is especially important for assuring that process specifications, conditions, sequencing, decision criteria, and formulas have been properly incorporated into the computer program..." Regarding this FDA policy, it is important to note that [CLIENT] has chosen the most prudent course of action for the clients they serve (i.e., those regulated by FDA) by developing a standard (off-the-shelf or configurable) software package that can be tailored (configured) to a client's specific requirements. By using this approach, it is the application-specific software, i.e., the client specific configuration, that requires the highest level of documentation, including a copy of the source code, and is subject to examination by FDA. For a configurable program such as the Version X.x software that is being developed by [CLIENT], documentation of the development and testing (primarily structural testing to provide assurance that the code logic is correct according to design requirements) of the software package, and allowing their clients to perform an on-site audit of their software development and validation program is sufficient to satisfy regulatory requirements.

Several of the SOPs reviewed as part of this assessment were found deficient to some degree, but again considering the youth of [CLIENT's] quality program, their progress at the time of the assessment was considered commendable. It was our recommendation that all current SOPs be evaluated in terms of the findings of the report and subsequently modified and/or supplemented if required. Supplementing, streamlining, and revising the current complement of SOPs covering the various aspects of development, testing and maintenance of computer/software systems will further strengthen the excellent foundation for software/system development and validation that [CLIENT] has established.

Generation of some additional procedures or guidelines was also recommended. One of the primary procedures recommended may be described as, "How to Write a Project Quality/Validation Plan." This would be one of the first plans developed during the concept phase of any project, to which all other quality and validation activities are subservient. The plan procedure would identify, for example, required elements for the Project Quality/Validation Plan, controlling procedures, quality and validation (Q&V) milestones, Q&V activities (audits, reviews, etc.), Q&V documentation, responsibilities, and points to implement change management and/or change control (both are elements of configuration managment). Generation of a guideline or plan (e.g., a generic quality plan) that delineated how to integrate the various development, testing, and validation tasks associated with computer-related systems would also significantly strengthen the current validation program by providing a common basis for executing all automation projects.

A key document that must be generated as part of the development/validation process for computer-related systems is a system definition or functional requirements document. FDA inspections are consistently begun with a request to see the definition or requirements document(s) along with a validation (or quality) plan. Without this document, an investigator cannot adequately determine the quality of the design documentation, or more importantly, if the testing was performed on the system "as wired, as installed, and as used." FDA has been very candid regarding their expectations for design documentation. Therefore, in our opinion, it is imperative that documents delineating a user's ([CLIENT's] customer) intended usage of [CLIENT's] manufactured systems be generated very early in the development process. This would represent a competitive advantage for [CLIENT].

It is our opinion that strengthening and supplementing the existing program for software development and testing, and computer validation will ultimately establish a comprehensive development/validation program for all computer-related systems manufactured and installed by [CLIENT]. It is suggested that a quality plan approach, an approach we have demonstrated to be very successful in the development and validation of computer-related systems and associated software, be utilized for validation of all automation projects. For current projects underway and other projects to follow, a project specific validation/quality plan that delineates all the necessary steps to appropriately develop and validate [CLIENT's] computer-related systems would also represent a significant competitive advantage. We have successfully utilized this methodology on several projects to assist in concurrent system/software engineering and validation. We recommend that [CLIENT] investigate this concept as a vehicle for developing the required functional requirements and other design specifications for all ongoing and future automation projects. This methodology has proven that validation can be accomplished in a shorter time frame, more efficiently, and at lower cost. We have experienced that a great deal of the superfluous detail often associated with undirected development and validation activities can be eliminated through the use of this methodology.

[CLIENT] should be made aware that "skid mounted" equipment or "packaged systems" with on-board PLCs, microprocessors, and/or loop controllers, or controlled by a PC such as the [CLIENT] system have been receiving increasing regulatory scrutiny. The reason for the increased scrutiny is that frequently this embedded automation is not very well documented and/or the automation aspects of the equipment are causing unexplained failures adversely affecting product quality. It has been our experience that many unexplained failures can be traced to on-board automation control systems or software that have not been sufficiently tested by the developer/manufacturer. Regarding documentation, the end-user often has no or incomplete documentation of software development and test results to present to a FDA investigator during an inspection in support of the validation of the embedded system. We strongly recommend that [CLIENT] provide their customers with a comprehensive documentation package as one of the deliverables included with their computer-related systems.

Conclusion

The Software Supplier Assessment Plan matrix presented in this article was developed to provide a format based on internationally accepted standards, and a consistent, semi-quantitative measure of a software supplier's capabilities (to aid in the selection process), and performance (following selection at predetermined points in the project life cycle). It has proven to be a very useful tool for assessments we have performed, but is not presented as, or intended to be, a universal tool that will cover all eventualities. It must be tailored to the specific needs of a given project and the internal requirements/procedures of the end-user company. The raw score for the assessment should not be used as the sole determinant for supplier selection or evaluation. Other factors such as the potential adverse impact of observed deficiencies on the end product (a validated computer system), the product/service being provided by the supplier, the maturity of the supplier's quality program, the overall fitness of the supplier's software development and testing program, and a supplier's willingness to improve, and progress in improving, in the areas found deficient must be considered in the overall evaluation process. ❑

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