Cleaning Validation Manual

A Comprehensive Guide for the Pharmaceutical and Biotechnology Industries

Syed Imtiaz Haider, Ph.D.

Erfan Syed Asif, Ph.D.

CRC Press
Taylor & Francis Group

Cleaning Validation Manual

A Comprehensive Guide for the Pharmaceutical and Biotechnology Industries

Cleaning Validation Manual

A Comprehensive Guide for the Pharmaceutical and Biotechnology Industries

Syed Imtiaz Haider, Ph.D.
Erfan Syed Asif, Ph.D.

CRC Press
Taylor & Francis Group
Boca Raton London New York

CRC Press is an imprint of the
Taylor & Francis Group, an **informa** business

CRC Press
Taylor & Francis Group
6000 Broken Sound Parkway NW, Suite 300
Boca Raton, FL 33487-2742

Printed in the United States of America on acid-free paper
10 9 8 7 6 5 4 3 2 1

International Standard Book Number: 978-1-4398-2660-7 (Hardback)

Visit the Taylor & Francis Web site at
http://www.taylorandfrancis.com

and the CRC Press Web site at
http://www.crcpress.com

Dedicated to my loving parents and family

Syed Imtiaz Haider

Dedicated to the fond memories of my late father, Syed Asif Moin, and

the affection of my mother, Roshan Jahan, who lit a fire

in me many years ago

Erfan Syed Asif

Contents

List of Figures

List of Tables

About the Book

The *Cleaning Validation Manual* provides technical solutions in both text and electronic form that fulfill the training needs of finished pharmaceutical manufacturers, active and nonactive pharmaceutical manufacturers, biopharmaceutical manufacturers, biotechnology contract laboratories, bioresearch and development laboratories, universities, and institutions offering cleaning validation courses and training.

The *Cleaning Validation Manual* with the CD-ROM is a valuable tool for both existing and new biotech manufacturers, finished pharmaceutical manufacturers, and active/nonactive API manufacturers. It is equally relevant to formulators, research and development managers, manufacturing production supervisors and operators, and quality assurance personnel involved in process realization.

The manual provides exclusive training guidelines in electronic form on a CD-ROM for customer convenience. This enables users to amend or adopt them with or without reinventing the wheel, thus resulting in time-saving and optimal resource utilization.

The ready-to-use *Cleaning Validation Manual* is based on general principles of cleaning and techniques provided on CD-ROM so that customers can input them into their computers and use their own Microsoft Word® program to edit and print these documents. The contents are written in simple language. The book will help to minimize the amount of effort, to avoid the nightmare of validation managers, development managers, production managers and R&D personnel trying to meet the regulatory training requirements within optimal time establishing in-house training programs. The *Cleaning Validation Manual* provides hands-on training information based on the current approach to using the appropriate technique effectively. It refers exclusively to principles and techniques applicable in the pharma industry and ensures product quality, potency, efficacy, and safety. Specific formats are used to describe the concepts step by step to ensure that the electronic files can be easily used worldwide with a diversified range of organizations involved in pharma and biopharmaceutical development, manufacturing operations, research & development, academic teaching, and professional development. Twenty-four cleaning protocol templates along with the cleaning procedures and more than 200 APIs with their toxicity and solubility levels have further added value to the book.

It is true that over the last few decades there has been significant advancement in the development of biopharmaceuticals. However, there is no single book that provides all of the following:

- A valuable ready-to-use cleaning validation manual
- Time saving for validation professionals
- Development of skilled manpower
- Ready-to-use cleaning validation master plans and procedures
- Cleaning procedure templates for over 20 extensively used pieces of manufacturing equipment
- Templates for the 12 most commonly used equipment in solid dosage form
- Templates for the 6 most commonly used equipment in liquid dosage form

- Templates for the 6 most commonly used equipment in the sterile area
- Matrix of toxicity and water solubility for over 200 APIs
- Reference to international regulatory compliance
- Reduced product development failures
- Prevention of reinventing the wheel
- Optimization of research expenses
- Avoidance of marketing delays
- Marketing edge over competitors
- Avoidance of incidental cross-contamination
- Improved company credibility
- Uninterrupted product supply
- Positive public opinion
- Improved process product safety
- Reduced product recalls
- Sampling tools for cleaning validation

The *Cleaning Validation Manual* is primarily written in a global context and can be beneficial to any industry interested in the development and manufacture of new APIs and to biosimilar and finished pharmaceutical manufacturers.

This book may be purchased for the following reasons:

- It provides readers and frontline healthcare products manufacturers, R&D management, and biotech laboratories with all the information they need to make a successful cleaning validation master plan and apply it.
- It is a simple, concise, and easy-to-use reference tool covering basic concepts and the elements of training required by educational institutions and professional certification bodies.
- The text (and CD-ROM) is a valuable time saver for companies that are in the process of developing manpower in order to achieve consistency in their operations.
- The topics provided in the CD-ROM can be easily tailored to incorporate changes of in-house training requirements.
- The topics provide stepwise guidance on how to train new and existing staff on cleaning concepts and increase awareness.

The *Cleaning Validation Manual* has the following advantages:

- It has been tested with proven results.
- It has been formally organized and published as a tool for the healthcare industry, covering diversified topics related to the cleaning validation master plan.
- It minimizes workload and increases efficiency.
- It does not merely provide guidelines or thought processes, but rather gives ready-to-use templates to develop master plans, SOPs, and validation protocols.

- It enables manufacturing companies to avoid hiring consultants for development of a cleaning validation master plan, worst-case matrices and protocols, and ultimately eliminating consulting fees.
- It serves as a single source to achieve and maintain a successful cleaning validation program.
- It is a practical guide that educates new and existing staff involved in routine operations.
- It is written in a global text and can serve as an effective tool for beginners.
- It reinterprets the list of specifics that need to be addressed to obtain a successful cleaning validation program.
- It provides an accurate and meaningful understanding of cleaning and the healthcare industry.

Preface

The FDA's concern with contamination of nonpenicillin drug products with those that contain penicillin and the cross-contamination of drug products with potent steroids or hormones are the main reasons behind the concept of cleaning validation in pharmaceutical industries. This has led to the formation of GMP regulations (part 133.4) in 1963, according to which all the equipment used in pharmaceutical industries to manufacture, fill, and pack drug products must be maintained in a clean and orderly manner. Of course, the main rationale for requiring clean equipment is to prevent the contamination or adulteration of drug products. Hence, the idea of cleaning validation in pharmaceutical industries is not new. The purpose of this manual is to provide a generic format for a Cleaning Validation Plan for pharmaceutical companies along with validation protocols for the most commonly used equipment in various manufacturing areas and their sampling points, using a pharmaceutical manufacturing site with both sterile and nonsterile operations as the case facility. The *Cleaning Validation Manual* has been organized as a database to train the manpower involved in the development, manufacturing, auditing, and validation of biopharmaceuticals on a pilot scale, leading to scaled-up production. Considerable thought, care, guides, and learning elements were forged to create the *Cleaning Validation Manual*.

Over the last decade, considerable information has been published referring to advancements in explaining the cleaning validation approach. Cleaning approaches are based on information provided in internationally recognized books and the author's own experience. This volume will serve as a valuable training reference guide that will be referred to repeatedly.

The *Cleaning Validation Manual* is divided into sections (CLV-1 to CLV-44).

Section CLV-1 gives a brief overview of how to establish a cleaning validation program, cleaning validation norms, advantages and disadvantages of using certain types of equipment, products, facilities, dosage forms, and the basic principles of products and equipment grouping.

In Sections CLV-2 to CLV-16, reference is made to introduction (of cleaning validation), scope and approach, cleaning validation team members and responsibilities, cleaning validation philosophy, strategies and methodology, planning phase, execution phase, analytical testing and reporting phase, equipment description, facility description, utilities description DI, WFI, steam, compressed air, utilities monitoring and microbiological control, equipment cleaning materials/detergent description, microbiological cleaning of equipment surface, solubility of active materials in water, and toxicity of active materials.

Sections CLV-17 to CLV-20.10 provide the cleaning validation product grouping matrix (tablet-capsule PPS), the product/equipment train matrix (tab-cap PPS), the worst-case product matrix (tab-cap PPS), and validation protocols with corresponding cleaning procedures (fluid bed dryer, mixer, granulation machines, powder bins, tablet press [three types], sieves, powder-filling machines, encapsulation machines [two types], film-coating machines, and sugar-coating machines).

Sections CLV-21 to CLV-23 provide the cleaning validation product grouping matrix (syrup), the product/equipment train, and the worst-case product for syrups.

The cleaning validation product grouping matrix, the cleaning validation product/equipment train, and the worst-case product for suspension are described in Sections CLV-24 to CLV-26.

Sections CLV-27 to CLV-29 refer to the cleaning validation product grouping matrix (drops), the product/equipment train, and the worst-case product in hypothetical drops.

Sections CLV-30 to CLV-32 refer to the cleaning validation product grouping matrix (cream/ointment), the product/equipment train, and the worst-case product for cream and ointment.

Sections CLV-33 to CLV-35 refer to the cleaning validation product grouping matrix (suppositories), the product/equipment train, and the worst-case product for suppositories.

Sections CLV-36 to CLV-36.4 provide validation protocols for manufacturing vessels, bin-washing stations, syrup-holding tanks, filling stations, and the filtration assembly.

Sterile area equipment cleaning validation is referred to in Sections CLV-37 to CLV-39.6 starting from the cleaning validation product grouping matrix (sterile product), the cleaning validation product/equipment train matrix, validation protocols, freeze dryer, mobile tanks, filtration assembly, preparation tanks, preparation vessel, and filtration and filling. Section CLV-40 refers to the cleaning validation tentative plan.

In Section CLV-41, a matrix is provided to document cleaning validation and sampling, and testing status. The regulatory guidelines of the Food and Drug Administration (FDA), United States Food and Drug Administration (USFDA), World Health Organization (WHO), and European Medicines Agency (EMEA) are referred to in Sections CLV-42 to CLV-42.4. Information about the sampling tools is provided in Section CLV-43. Recommended readings are provided in Section CLV-44.

The ready-to-use Cleaning Master Validation Plan and protocols in combination with the regulatory guidelines provide a good source of training material for experienced and inexperienced practitioners in pharmaceutical and biotechnology industries.

Pharmaceutical industries are regulated worldwide to be in compliance with Current Good Manufacturing Practices (CGMP) and Good Laboratory Practice (GLP) principles, with particular focus on cleaning validation and cross-contamination issues.

The Cleaning Master Validation Plan and 24 protocols can be downloaded from the CD and adopted directly or with minor changes. The ready-to-use protocols allow end users to record all raw hard data.

Each company is required to create a definite cleaning matrix based on the product mix. The Cleaning Master Validation Plan and protocols available in this manual enable end users to understand the principles and elements of the cleaning approach and sampling techniques and provide documentation language ranging from the generic to the specific.

Compliance with FDA regulations is essential for companies intending to export their products to the United States and Europe. As a result, only a few companies are able to seek approval for export, one of the reasons being the absence or inadequacy of a Cleaning Master Validation Plan.

The information provided in the CD-ROM includes valuable tools for active pharmaceutical ingredients that are used in developing matrices for a cleaning Validation Master Plan to achieve FDA, GMP, ICH, EMEA, and GLP compliance. The manual is especially relevant to trainers, quality assurance personnel, engineers, validation designers, internal and external auditors, technical training managers, and anyone interested in developing a cleaning qualification documentation matrix in the healthcare industry.

Dr. Syed Imtiaz Haider

Acknowledgments

I am grateful to Dr. Ayman Sahli, the general manager of Gulf Pharmaceutical Industries, for always encouraging me in my professional achievements and continuously keeping me motivated.

I thank my friends and colleagues for their help and encouragement and for creating a professional environment. I am also indebted to my wife, Syeda Shazia Fatima; my son, Syed Zeeshan Haider; and my daughter, Syeda Mehreen Fatima, for their patience while I compiled this book. I am extremely thankful to Dr. Syed Erfan Asif for showing due diligence in the resourcing of literature and in the preparation of the manual.

Finally, special thanks are due to the staff of Taylor & Francis Group for their patience and diligence in the production of this book.

Dr. Syed Imtiaz Haider

I take pride in acknowledging my heartiest sense of gratitude to Dr. Syed Imtiaz Haider, for not only granting me the opportunity to author this book with him but also for his sterling guidance, valuable support and inspiring encouragment.

I am indebted to my wife, Dr. Beena Asif, and wish to pay my special thanks for extending her best cooperation during the writing of this book, for providing me the finest possible atmosphere and demonstrating endurance during the lovely summer evenings that were spent compiling the book instead of sitting in the serenity of the living room and commenting on interesting television programs. Of course, my children, Rija Asif, Usman Syed Asif, and Umer Syed Asif, have no less importance in this regard. I would like to pay my sincerest thanks to A. Hashmi for compiling the pictures of equipment for the validation protocol templates. My colleague Dr. Syed Vakil Ahmed holds an equally significant role because of his encouragement and compassion while writing this book. They all remain deep-rooted in my heart for all time.

Dr. Erfan Syed Asif

Authors

Syed Imtiaz Haider earned his PhD in chemistry and is a quality assurance and environmental specialist with over 20 years experience in aseptic and nonaseptic pharmaceutical processes, equipment validation, and in-process control and auditing. Dr. Haider is currently involved in several major biotechnology-based tasks, including cell-line qualification, process validation, bioanalytics, method validation, biosimilar comparative studies, organizing preclinical studies, and preparing the Central Technical Dossier (CTD) formatted for regulatory submission. Dr. Haider is the author and coauthor of more than 20 research publications in international refereed journals dealing with products of pharmaceutical interest, their isolation, and structure development. A professional technical writer, Dr. Haider has authored more than 2000 standard operating procedures based on FDA regulations, ISO 9001:2000, and ISO 14001:2004 standards. He is a certified Quality Management System (QMS) auditor of International Register of Certificated Auditors (IRCA) and a registered associate environmental auditor for Environmental Association of Registered Auditors (EARA). He has written more than 10 quality system manuals for multidisciplinary industries and provided consultancy to the Drug Control Laboratory of the Ministry of Health in the United Arab Emirates in developing a quality management system based on ISO 9003 and later transition to ISO 9001:2000.

Dr. Haider works as a quality affairs director at Julphar, Gulf Pharmaceutical Industries, and is involved in the preparation of several abbreviated new drug application (ANDA) files, which, after successful FDA, EU, and GMP inspections, will lead to the export of finished pharmaceutical products to the United States and European markets. He has also written *ISO 9001:2000: Document Development Compliance Manual: A Complete Guide and CD-Rom* and *Pharmaceutical Validation Master Plan, The Ultimate Guide to FDA, GMP, GLP Compliance and Validation Standard Operating Procedures and Biotechnology: A Comprehensive Training Guide for the Biotechnology Industry*. Dr. Haider holds the intellectual copyright certificate of registration on an electronic documentation package on ISO 9000 and ISO 14001 from the Canadian Intellectual Property Office. He is also a contributing author of chapters on ISO 9001:2000 and ISO 14001 in international publications.

Dr. Haider has organized cGMP conferences in the region, resourcing competitive speakers from Europe, Canada, and the United States.

Erfan Syed Asif earned his PhD in organic chemistry and has expertise in various areas under the quality operations umbrella with 15 years of experience in pharmaceutical industries in Asia and North America. Dr. Asif currently holds the position of quality control manager in Gulf Pharmaceutical Industries. He has vast experience working in the U.S. FDA and Health Canada approved facilities in managerial positions, where his responsibilities included the administrative routine of the quality control laboratory, investigating and responding to market complaints, advisory to production and introduction of new products, and conducting annual requalification of analytical instruments. Dr. Asif has extensive experience in overseeing qualification projects for manufacturing equipment, utilities, systems, sterilization techniques, aseptic processes simulation, and sterile and nonsterile products manufacturing processes.

As a validation consultant he provided guidance on projects at Pharmacia Upjohn (Michigan), Glaxo Smith Kline (Canada), and Air Liquide, Canada (medical gas manufacturers) based on Health Canada and U.S. FDA regulations. He also provided extensive validation training to groups of validation specialists working in Canada and the United States.

Dr. Asif is the author of many research publications in various internationally published chemistry journals and conference proceedings.

Dr. Asif is also a regular appointee of the Board of Advanced Research and Studies of Karachi University, Pakistan, as an external examiner for thesis evaluation and *viva voce* of M.Phil and PhD degrees in pharmaceutical chemistry.

Introduction

This *Cleaning Validation Manual* was designed and written with particular focus on pharmaceutical, biopharmaceutical, and active pharmaceutical manufacturing industries. It is for cleaning task executors, training managers, trainees, entry-level technicians, production managers, quality assurance managers, quality system auditors, research and development formulators, consultants, and supervisors (who are responsible for production and process control and maintaining a documented Cleaning Master Validation Plan) to ensure successful operational controls and prevent cross-contamination. It provides a cleaning validation approach and protocols that can be used to manage and document critical and noncritical cleaning tasks.

The numbering of sections and related course text is from CLV-1 to CLV-43. Each section number is assigned subsection numbers when applicable (CLV-20.1, CLV-36.1, CLV-39.1 to CLV-42.1) to provide specific details. In addition to this, the reader may also update the cleaning validation matrix approach and modify protocols as required.

Disclaimer

Every effort has been made to ensure that the contents of the *Cleaning Validation Manual* and protocols are accurate and that recommendations are appropriate and made in good faith. The authors accept no responsibility for inaccuracies or actions taken by companies subsequent to these recommendations.

The similarity of the contents in the cleaning validation master plan and the protocols may be incidental because of similarity in principle.

CLV-1

How to Establish a Cleaning Validation Program

1.1 Cleaning in Finished, Biopharmaceuticals, and Bulk Chemicals

Finished pharmaceuticals exist in a broad range of dosage forms, which include solid, semisolid, liquid, aerosols, and parenteral formulations. Often a large number of product types of several different strengths are manufactured in one facility. This necessitates the use of special precautions to prevent product-to-product carryover. One of the strategies designed to prevent cross-contamination is cleaning. The number of cleaning procedures, assays, and equipment types are often overwhelming. Using nondedicated equipment is a common practice among pharmaceutical industries. This creates further obstacles to meeting the objective of cleaning, and thus establishment of a cleaning validation program applicable to all products becomes a great challenge.

In biopharmaceuticals, the presence of a large number of contaminants such as cellular remains, media constituents, waste products of cellular metabolism, and buffer salts generated during manufacture are factors that cause extensive problems in cleaning. Identification of the residues is often difficult because they may vary from batch to batch. For example, the presence of a large variety of proteinaceous materials in the residue makes the differentiation of contaminants from one another a challenge. In the case of mammalian cell cultures, because of the nature of the source material, microbial contamination is of great concern. Multiproduct facilities further give rise to concerns for regulatory agencies.

The contaminants, which need to be cleaned from a bulk chemicals manufacture process, include precursor molecules, by-products, intermediates, and other forms of impurities. Manufacture processes of bulk chemicals are typically biochemical or chemical syntheses carried out on a large scale. These bulk chemicals are later used as active ingredients in a finished dosage form pharmaceutical. The bulk chemical manufacturing process is usually enclosed in large tanks and includes the direct transfer of materials from tank to tank after each particular reaction or process. In most cases, the involvement of closed systems is due to the use of strong reagents and chemicals. This gives rise to the need of either automated or semiautomated clean-in-place (CIP) technologies. Problems in the cleaning procedure validation often arise from the lack of direct sampling from many areas of the closed systems.

Keeping in view the struggle that pharmaceutical and biotechnology industries have in dealing with cleaning validation, an approach that establishes a comprehensive cleaning validation is required.

1.1.1 Cleaning Program Norms

The cleaning procedures used in a facility can unveil important factors regarding process control, process reproducibility, sample collection procedures, and ways of monitoring the efficacy of cleaning procedures. Before establishing the cleaning program, it is significant

to first characterize the types of cleaning that are used in the facility. Cleaning methods used in the facility can tell us about the factors related to process reproducibility, process control, how to challenge the process, how to collect samples, and the best ways of monitoring cleaning efficacy during cleaning.

1.1.1.1 Cleaning Methods

1.1.1.1.1 Automated and Manual Cleaning

Although manual cleaning is a normal practice in the pharmaceutical industry, yet the use of automated cleaning usually provides reproducible results. The control system has integrated with it process control and process monitoring. The automated system is validated by challenging, and it is required that the cleaning cycle is proved to be rugged and provides reproducible results under a given range of operating conditions. The controls of an automated cleaning system also become part of the cleaning validation. Sometimes the design and construction of equipment make manual cleaning a necessity. In order to maintain good control over manual cleaning, the following parameters need to be regulated as a minimum:

A. Operator's training
B. Cleaning procedures
C. Good visual examination of the equipment
D. Change control programs

Ruggedness of the method can also be given emphasis in manual cleaning; however, reproducibility depends on strict adherence to the cleaning procedures.

1.1.1.1.2 Clean in Place and Clean Out of Place

The CIP system involves the cleaning of large pieces of equipment at its permanent location in a configuration very similar to that utilized for production. The process is quite similar to automated cleaning, where the control system also becomes part of cleaning validation. Usually, a computer validation part becomes integrated with it if CIP is based on programmable logic control (PLC). On the other hand, smaller equipment may be transported to a designated wash area where cleaning is performed. This practice is known as clean out of place (COP). Transportation to and from the wash area, component identification, potential of cross-contamination during transfer, and storage prior to use make the task of COP more challenging than CIP. However, using automated wash systems for COP reduces the differences between CIP and COP to a significant extent, mainly due to reproducibility of the results.

1.1.1.2 Equipment

1.1.1.2.1 Dedicated and Nondedicated Equipment

In pharmaceutical industries, dedicated equipment is used for the production of only a single product. This practice markedly reduces the chances of cross-contamination. Where the same equipment is used for the production of a range of products, the prevention of cross-contamination between products becomes the main challenge in the cleaning validation effort. Dedicated equipment should be clearly identified so as to prevent potential errors during cleaning and preparation. Nevertheless, cleaning nondedicated equipment represents a clearer impediment to overcome.

The cleaning of dedicated and nondedicated equipment also gives rise to concerns. CIP systems are often used for more than one tank in a facility. Special care needs to be taken in designing CIP systems. By using appropriate valving and backflow prevention, cross-contamination can be prevented. Similarly, any circulation within the CIP system should be constructed carefully and monitored closely during routine cleaning.

1.1.1.2.2 Minor and Major Equipment

Although there is no such terminology as minor equipment used in current good manufacturing practices (CGMPs), items such as utensils may be regarded as minor equipment. Major equipment represents those that play a central role in production processes. Typically, the cleaning of major equipment will be the subject of specific standard operating procedures (SOPs) and it is important to differentiate those pieces of equipment that are central to the production process from those that perform a secondary role (utensils). Material of construction should be of significant importance when establishing a cleaning validation program. CGMPs 211.65 emphasizes the material of construction as well as any substance required for operation, in which contact components, in-process materials, or drug products shall not be reactive so as to alter the safety and efficacy of the product beyond established requirements.

Equipment should not demonstrate any type of reaction with process materials, which contact them. Equipment with porous surfaces, for example, filters, filter bags, fluid bed dryer bags, membrane filters, and so on, will require thorough assessment while reviewing cleaning validation evaluations so as to ensure adequate product removal and minimize the potential for cross-contamination.

1.1.1.2.3 Noncritical and Critical Site of Equipment

Locations that have a tendency to endanger a single dose with a high level of contamination are called critical sites. Such locations or sites demand special cleaning emphasis. Besides ensuring that enough details are included in the cleaning procedure, the risk can be further reduced or completely eliminated by using more intensive sampling and testing plans. A more stringent acceptance criterion must also be established in this case to ensure effective cleaning validation.

1.1.1.2.4 Nonproduct Contact versus Product Contact Surfaces

As a matter of course, cleaning validation mainly focuses on product contact surfaces. However, in order to be more effective, programs for the elimination of cross-contamination must also address nonproduct contact surfaces. When establishing the prerequisites for nonproduct contact surfaces, the probable interactions of that area with the process must also be reviewed. This is important in order to make the cleaning program more effective.

1.1.1.2.5 Equipment Train: Simple and Complex

The group or collection of equipment or systems jointly functioning to carry out the production processes for a product is generally called "equipment train." There is a direct relationship between the complexity of cleaning validation and the complexity of the equipment train. The greater the pieces of equipment in the train, or the transfers of material involved in the process, the higher the complexity of cleaning validation.

1.1.1.3 Product

1.1.1.3.1 Low- and High-Risk Drugs

The pharmacological activities of drugs have a significant impact on the cleaning validation program. Materials of lower pharmacological activity do not have major issues in setting residual limits for cleaning validation. However, there are numerous materials and formulations where even minute quantities can have pharmacological activity. In such cases, although the equipment and cleaning procedures might be the same, tighter limits will be required for products with known adverse effects. Besides this, sampling and analytical methods also need to be refined to a high degree of sensitivity to ensure the removal of residue from equipment.

1.1.1.3.2 Solid and Liquid Dosage

The approach for cleaning equipment utilized for different dosage forms is significantly different. The difference is related to how contamination can be left on equipment and mixed with subsequent products. This can be understood by taking the following example: liquid product has a greater ability to penetrate equipment seals and joints, whereas solid product can form tufts or clumps on the surface, which may prevent wetting of that part by cleansing agents and thus inhibit the ability to rinse the residues properly. The same phenomenon can be true for the dispersion of contaminant on the surface of the equipment for solid and liquid products. The distribution of contaminants in the case of solid products may vary from point to point while that in liquid products is uniform across the surfaces.

1.1.1.3.3 Soluble and Insoluble Ingredients

The removal of insoluble materials from the equipment surface represents yet another difficult scenario because it requires more physical means as compared to soluble materials (active or excipient), which are often easily removed by solubilizing the product. The removal of insoluble or less soluble materials by adding cleaning agents results in increased wetting and solvation of the materials.

1.1.1.3.4 Sterile and Nonsterile Facilities

Sterile manufacturing facilities differ from nonsterile ones because of the extra precautions required to control microbial and endotoxin levels. In nonsterile products, environmental concerns are reduced but are still important. This is because objectionable microorganisms are also common in oral liquids and topical, similar practices are required to minimize these organisms here.

1.1.1.4 Facility

1.1.1.4.1 Single-Product Facility and Multiple-Product Facility

The scenario is equivalent to that for dedicated and nondedicated equipment. Since no cross-contamination concerns exist in the case of a facility producing only a single product, the validation requirements are automatically minimized. Various challenges related to multiproduct facilities, which need to be dealt with, are elimination of cross-contamination potentials and careful monitoring of changeover of equipment from one product to another. In addition, continuous monitoring must also be warranted to ensure that all controls and limits established are in place after accomplishment of cleaning validation.

1.1.1.4.2 Campaign Production and Batch Production

Campaign production always helps in minimizing cross-contamination issues between lots. In a multiple-products facility, campaign lots of a single product or product family are produced in the same equipment. At times, the production trot may be stopped for a part cleanup of the equipment, which is less stringent than a full cleanup. Once the campaign production is over, an intensive cleaning of the facility and equipment can be performed before starting the production of a different product.

1.1.2 Cleaning Validation

A master plan is the basis of the cleaning validation program, which describes the overall approach of cleaning validation. This includes the matrixing philosophy involved and the rationale associated thereto. Once the products and pieces of equipment are identified for use in the validation study, trials may start.

Some worst-case scenarios may also be considered to challenge the cleaning procedure, for example, having the product dried on the surface to make the cleaning difficult or applying the effect of weekends and holidays on the cleaning schedule, and so on.

A brief review of the activities to establish a comprehensive cleaning validation program is given below.

1.1.2.1 Cleaning Validation Program

a. *Product grouping:* Based on formulation and dosage form, potency, toxicity, and solubility, all products are grouped. The broad groups may then be divided into subgroups according to formulation and process types. After the grouping, the worst-case product is selected from each group. The worst-case product from each group may be the least soluble, the most toxic, or with the highest concentration of active ingredients. However, there is no hard and fast rule for the selection of worst-case products. In some situation, a combination of these parameters may also be used.
b. *Equipment grouping:* Equipment of similar design and function is typically collected in one group for validation study. In case of similar cleaning procedures implemented, validation can be conducted on the largest- and smallest-scale equipment separately.
c. *Cleaning methods grouping:* The grouping of cleaning procedures may be appropriate; however, the validation of the cleaning procedure may also be conducted independently of the equipment for which it is used.
d. *Cleaning agents grouping:* Systems may also be subdivided on the basis of cleaning agents utilized on those systems when considering product formulation and equipment groupings. Incidentally, the use of a single cleaning agent will greatly minimize the work required to determine if residues of the agent remain after cleaning.

1.1.2.2 Residues and Residue Removal

a. *Types of residues:* Physical and chemical properties such as solubility, hydrophobicity, and reactivity of residues affect the ease with which they are removed from surfaces. It is therefore important to first identify the substance to be cleaned.

b. *Cleaning agents:* It is necessary to know the ingredients of a cleaning agent. This is important because when cleaning agents are used to aid cleaning, their removal must also be demonstrated to ensure the proper cleaning of surfaces. Once the ingredients are known, validation personnel must then determine the worst-case ingredient in the cleaning agent.

1.1.2.3 Cleaning of Equipment

a. *Types of cleaning processes (manual/semiautomated/automated):* The direct cleaning of equipment by a trained operator is considered manual cleaning. Among the critical parameters involved in manual cleaning are volumes of cleaning agents and rinse water, temperature of wash and rinse solutions, duration of washing cycle, concentration of detergent used, and so on. In semiautomated cleaning, various levels of automatic control are also included. This may also be considered as a blend of manual and automated cleaning, for example, manually removing gaskets and fittings before automated CIP or dismantling a pump prior to cleaning in an automated COP system. The automated system usually comprises programmable cycles and does not include personnel intervention.

b. *CIP/COP:* As discussed in the sections above, CIP generally refers to the automated circulation system. Some of the critical aspects of the CIP system that need to be considered are the certainty of preventing backflow and of assessing the suitability of recirculated cleaning solution for subsequent use. CIP parameters such as flow rate, pressure, and spray ball patterns must also be qualified prior to use.

c. *Equipment design considerations:* Care must be taken in designing equipment to minimize the risks of cross-contamination and microbial contributions to the equipment. Preferably, equipment should be constructed of a nonreactive material. If the cleaning agents seem to be reactive with sealants, plastics, or filters, then design specifications and preventative maintenance procedures must be carefully looked into.

d. *Equipment storage after cleaning:* It is necessary to protect equipment from cross-contamination between the period of cleaning completion and reuse for the next product manufacture. Areas must be allocated for this purpose where possible cross-contamination may be controlled. In the meantime, records must also be maintained showing equipment numbers, date and time of cleaning, and names of persons who cleaned and inspected it.

1.1.2.4 Cycle Development

a. *Cleaning agent selection:* Selection criteria for cleaning agents should be the suitability of removing product residues and low toxicity. Besides these, ingredients of the selected cleaning agent should also be known so that the cleaning of reagent itself can be proven.

b. *Cleaning parameter selection:* The most important cleaning parameters are time, temperature, cleaning agent concentration, and cleaning action, for example, impingement, sheeting, rinsing, and so on. By evaluating each cleaning step, the removal of residues can be determined and thus the need to add, delete, or modify a cleaning step can be decided as well.

c. *Standard operating procedures:* A draft-cleaning procedure should be in place prior to starting the cleaning validation. Once a successful validation is accomplished, the final standard operating procedure for cleaning must be completed with details such as time, temperature, concentration, and cleaning action.

d. *Operator training:* A formal training of operators includes reviewing and understanding the cleaning SOPs, qualified apprenticeship, and ensuring that training is successful. Operators must also understand the process of cleaning and the equipment they are cleaning.

1.1.2.5 Sampling Techniques and Analytical Methods

a. *Swabs and wipes:* Swabs and wipes are widely accepted sampling techniques. Their advantages are that they dissolve and physically remove samples, are economical, allow sampling of the defined area, are usable on a variety of surfaces, and are applicable to active ingredients, microbial and cleaning agents. However, there are some limitations involved with swabs and wipes: for example, they may introduce fibers and material to the sampling area; sometimes the design of the swab may also inhibit the recovery and specificity of the method; and they are difficult to use in crevices, pipes, or large vessels.

b. *Rinse sampling:* The advantages of rinse sampling are the following: ease in sampling, coverage of large areas in samples including sampling of unique surfaces, being adaptable to on-line monitoring and fewer technicalities involved than swabs, and so on. Restrictions include a possible decrease in test sensitivity, inability to detect residue locations, inadequate homogenization of residues, and minimum information about actual surface cleanliness in some cases. Due to the criticality of rinse volume, usually the entire piece equipment is used for rinsing, such as a vessel.

c. *Direct surface monitoring:* The benefits of direct surface monitoring are that it is fast, noninvasive, and economical. There are some limitations however; for example, there are some prejudices and some techniques are not available yet. Visual examination of equipment for cleanliness immediately before use is a requirement by CGMP regulations. It is a form of direct surface analysis. Other commonly used methods of monitoring include pH, conductivity, total organic carbon (TOC) titration, high-performance liquid chromatography (HPLC), thin-layer chromatography (TLC), capillary zone electrophoresis, Fourier transform infrared (FTIR), atomic absorption, ultraviolet (UV) spectrophotometry, and so on.

1.1.2.6 Limits and Acceptance Criteria

The most important element of a good cleaning validation program is the determination of limits and acceptance criteria. When determining the limits, care must be taken so that they are achievable by the analytical methods available for the specific product and active ingredient, are practical for the actual cleaning situation to be validated, and are scientifically rationalized and verifiable.

The most commonly used basis for setting the acceptance limit is a mathematical calculation that allows a certain therapeutic dose to carry over into each dosage unit of the next product. The actual numerical limits are based on the pharmacological potency of the product, the toxicity of the residue, and the analytical limit of detection.

1.1.2.7 Ongoing Monitoring of Cleaning

Besides inspection of each piece of equipment to ensure cleanliness before use, additional verification can also be done. This depends largely on the complexity of the equipment. Automated cleaning methods may not require ongoing verifications; however, semiautomated processes and manual cleaning usually need periodic verification and determination about the reproducibility of the process over time.

1.1.2.8 Change Control

Changes made to cleaning SOPs, analytical methods, detergents, equipment, product formulation, etc. should fall under the auspices of the change control policy of the company. Formal documentation will be required to make changes to these items. Changes performed under the change control policy will require reconfirmation of the original cleaning validation results. In case the change is deemed to be fundamental to the grouping philosophy or to the cleaning method, the change may require a revalidation, which may differ from verification only by the amount of sampling.

CLV-2

Introduction

Your Company's Logo

Your Company's Name

2.1 Cleaning Validation

Cleaning validation ensures the implementation of an efficient cleaning procedure, which excludes "cross-contamination" between different products or different batches of the same product.

Another definition of the concept of cleaning validation, which is controlled through a separate master plan, is a tool that provides documented evidence that a cleaning procedure is effective in reducing, to predefined maximum allowable limits, all kinds of contamination from an item of equipment or a manufacturing area following processing. The means of evaluating the effectiveness of cleaning will involve sampling cleaned and sanitized surfaces and verifying the absence of product residues, cleaning residues, and bacterial contamination.

Regulatory agencies as well as pharmaceutical industries have placed a great deal of emphasis on the validation of cleaning procedures during the last decade. Various agency documents have clearly established that cleaning procedures should be validated.

In order to prevent contamination, Food and Drug Administration (FDA), in its 1963 GMP Regulations (Part 133.4), stated, "Equipment shall be maintained in a clean and orderly manner." A very similar section on equipment cleaning (211.67) was included in the 1978 CGMP regulations.

FDA emphasizes on the validation of the cleaning procedures, particularly in cases where contamination of materials poses the greatest risk to the quality of drug products. Validation of cleaning procedures should reflect actual equipment usage patterns. If a number of products are manufactured in the same equipment and the same procedure is used to clean the equipment, a worst-case product can be selected for validation purposes based on the solubility and difficulty of cleaning and the calculation of residue limits based on potency, toxicity, and stability.

A descriptive protocol should be available to indicate the type of samples to be obtained. The sampling method used may be swab, rinse, or direct extraction, as appropriate, to detect both insoluble and soluble residues. The sampling methods used should be capable of quantitatively measuring the levels of residues remaining on equipment surfaces after cleaning.

2.1.1 U.S. FDA Guidelines

FDA, in its guidelines for cleaning validation, has clearly expressed expectations that industries have to fulfill. The basic requirements, as per FDA, are as follows:

1. A written procedure on how cleaning processes will be validated
2. Clearly outlined responsibility for performing and approving validation study, acceptance criteria, and revalidation requirement
3. Approved written protocols describing the study to be performed, system or piece of equipment, sampling procedures, testing methods, and so on
4. Execution of the protocols in accordance with the written commitment and recording of the results
5. A final validation report with all available data, duly approved by higher management, declaring whether or not the process has been successfully validated

2.1.2 Health Canada Guidelines

According to Health Canada, the objectives of the cleaning validation are as follows:

1. One should verify the effectiveness of the cleaning procedure for removal of product residues, degradation products, preservatives, excipients, and/or cleaning agents so that analytical monitoring may be reduced to a minimum in the routine phase.
2. Cleaning procedures must strictly follow carefully established and validated methods.
3. Appropriate cleaning procedures must be developed for all product-contact equipment used in the production process. Consideration should also be given to non-contact parts into which product may migrate (e.g., seals, flanges, mixing shaft, fans of ovens, heating elements, etc.).
4. Relevant process equipment cleaning validation methods are required for biological drugs because of their inherent characteristics (proteins are sticky by nature), parenteral product purity requirements, the complexity of equipment, and the broad spectrum of materials that need to be cleaned.
5. Cleaning procedures for products and processes that are very similar do not need to be individually validated. This could be dependent on what is common, equipment and surface area, or an environment involving all product-contact equipment.

2.1.3 EU-GMP Guidelines

The European Union guidelines also describe cleaning validation in the following way:

1. Cleaning validation should be performed in order to confirm the effectiveness of a cleaning procedure. The rationale for selecting limits of carryover of product residues, cleaning agents, and microbial contamination should be logically based on the materials involved. The limits should be achievable and verifiable.

2. Validated analytical methods with the sensitivity to detect residues or contaminants should be used.
3. The detection limit for each analytical method should be sufficiently sensitive to detect the established acceptable level of the residue or contaminant.
4. Normally only cleaning procedures for product-contact surfaces of the equipment need to be validated. Consideration should be given to no contact parts. The intervals between use and cleaning as well as cleaning and reuse should be validated. Cleaning intervals and methods should be determined.
5. For cleaning procedures for products and processes, which are similar, it is considered acceptable to select a representative range of similar products and processes. A single validation study utilizing a "worst-case" approach can be carried out, which takes account of critical issues.
6. Typically, three consecutive applications of the cleaning procedure should be performed and shown to be successful in order to prove that the method is validated.

The World Health Organization (WHO) also emphasizes on the validation program of cleaning procedures under clause 4.11 of Quality Assurance of Pharmaceuticals—A compendium of guidelines and related materials—volume 2 updated and revised edition—Good Manufacturing Practices and Inspection (WHO-2003)—in the following words:

> It is of critical importance that particular attention is paid to the validation of analytical test methods, automated systems and cleaning procedures.

Looking into the clauses established by various authorities, cleaning validation can be defined as "A documented proof of consistent and effective cleaning of pharmaceutical or food systems or equipment to predetermined limits so as to prevent contaminants from leaving residues that may adulterate and adversely affect the safety and quality of the next product manufactured."

Cleaning validation projects are separately governed under protocols that reference background documentation relating to the rationale for "worst-case" testing, where this is proposed. The protocols further explain the development of acceptance criteria, including chemical and microbial specifications, limits of detection, and the selection of sampling methods.

2.2 Validation Master Plan

The validation master plan (VMP) is a crucial document because it describes the basic concept for the overall site validation program. It is basically the blueprint for a successful validation project. It defines one's approach to validation, applicable references, and requirements of the GMP system. VMP describes the approach to training, procedures for deviation management, and change control, and establishes responsibilities for the entire

validation project. Equipment processes, cleaning procedures, and relevant analytical tests are listed together with the foreseen protocols for their qualification or validation.

The cleaning validation master plan (CVMP) is intended to be a "live" document that supports the fundamental structure of any manufacturing facility, its equipment and instruments, subsequent operation, and maintenance and cleaning of the equipment for its lifespan for any active pharmaceutical ingredient.

CVMP should present an overview of the entire cleaning validation operation. The core of VMP is the matrix of equipment in the facility, the list of items to be validated based on the matrix, the worst-case scenario, and the planning schedule.

CVMP further provides the basis for validation required for CGMP compliance. This enables any sterile or nonsterile medicinal product that is produced, processed, stored, or distributed, by the manufacturing unit, to be validated for the effectiveness of the cleaning procedure thereof for any related manufacturing equipment under the control of an appropriate quality system.

VMP should provide a cross-reference to other documents, such as SOPs, validation protocols, validation reports, and equipment/product. A rationale for the inclusion or exclusion of validations from the approach adopted is also included.

CLV-3

Scope and Approach

Your Company's Logo **Your Company's Name**

A thorough validation of cleaning procedures for equipment and facilities will be conducted and accomplished based on matrices and a worst-case scenario as per this master plan.

This VMP covers the validation of cleaning procedures used at ABC Pharmaceutical Company. The scope of this plan addresses validation requirements to prove the efficacy of cleaning methods to remove residual drug products and microbial bio-burden to below predetermined limits.

CVMP will ensure that the cleaning approach of ABC Pharmaceutical Company is consistent with accepted industry practices and published health-based guidelines of the FDA and European Regulatory Agencies.

The cleaning validation approach will include, but not be limited to, the following:

- Identification of worst-case situations and development of a worst-case scenario to be used to evaluate cleaning procedures for the equipment train based on the nature of the cleaning methods used, the product and optimal equipment coverage, and the experience of the production staff responsible for day-to-day cleaning
- Utilization of a combination of visual examination, swab testing, and rinse water sampling for evaluating equipment cleanliness; development of acceptance criteria of the cleaning procedure by product/manufacturing and equipment and facilities (selected areas)
- Development of cleaning procedures that remove residual products to below levels of concern and remove the threat of product cross-contamination
- Review of existing equipment cleaning SOPs (for completeness, clarity, removing misinterpretation, and standardization)

A summary of the Cleaning Validation Matrix for all products manufactured at ABC Pharmaceutical Company's facility is presented in Matrix I. Details of the matrix as well as the equipment train in relation to bulk batch processes are presented in Matrix II.

CVMP includes the following:

- Organization of all validation activities
- Identification of the products/processes to be validated
- Specific cleaning process considerations

- Validation approaches
- Key acceptance criteria
- Documentation requirements
- General sequencing and prioritization of validation activities

The information contained in this plan may change as its realization progresses. Besides, it shall be reviewed annually to ensure that it remains current with existing processes, equipment/facilities, and policies. All previous versions of the CVMP shall be kept on file for reference. A validation schedule shall be maintained and kept up to date to accurately reflect the current validation status.

CLV-4

Cleaning Validation Team Members and Responsibilities

Your Company's Logo **Your Company's Name**

This master plan presents a medium in which the department concerned with completing the cleaning validation can mutually ensure regulatory compliance. The management (and/or designate) of production, quality control (chemical and microbiology), packaging, quality assurance, and validation will

- Agree on the requirements of the CVMP prior to implementation
- Discuss/determine the validation approach for completing each segment of the CVMP
- Direct the integration and maintenance of the CVMP

4.1 Specific Responsibilities

The specific responsibilities of departments and individuals supporting the cleaning validation are as follows.

4.1.1 Validation Department

A validation officer coordinates the entire validation process by scheduling meetings and discussions with the validation team, preparing the validation protocols, monitoring the validation process, compiling and analyzing validation data and test results, and preparing the final report. All documentation associated with validation should be reviewed and approved by the validation manager for completeness and compliance with CGMP requirements.

The validation officer will also develop an ongoing monitoring program (wherever applicable) to demonstrate that the processes are being maintained under control, and will support/advise on the creation and updating of all relevant systems and validation SOPs.

4.1.2 Production

A validation team member from the Production department participates in performing the validation steps during manufacturing processes and equipment qualification. This

department should prepare the necessary SOPs for the new process or equipment and assist in the collection of validation data.

4.1.3 Packaging

A validation team member from the Packaging department participates in performing the validation steps during the cleaning validation of packaging equipment. The Packaging department should prepare the necessary SOPs for the cleaning of new packaging equipment and assist in the collection of validation data.

4.1.4 Utilities/Calibration/HVAC

A validation team member from the Maintenance department participates in performing the validation; defining the necessary equipment specifications, limitations, capacity, calibration, and maintenance requirements; and providing the necessary training on the cleaning and proper operation and maintenance of the equipment. The Maintenance department is responsible for providing the necessary utilities and equipment accessories required during the validation process. The Maintenance department is also responsible for informing the relevant departments in advance of any anticipated change to the manufacturing equipment/new inclusion and for completing equipment surface area calculations with the help of relevant drawings.

4.1.5 Quality Control

A validation team member from the Quality Control (QC) department is responsible for providing the necessary support for the testing and reporting of test results for validation. A support group in QC should also perform microbiological testing and environmental monitoring during the validation process. The QC department provides swabs and surface recovery data for active ingredients and cleaning agents.

4.1.6 Quality Assurance

A validation team member from the Quality Assurance department will be responsible for reviewing and approving the validation protocol, providing necessary support, as and when required, making an assessment in case of deviations and excursions from the protocol, and reviewing and approving the final validation report.

4.1.7 Product Development Laboratory

A validation team member from the Product Development Laboratory is responsible for defining the process (new product or process) to be validated and for providing technical assistance to the validation team by defining specifications, limits, and manufacturing methods.

CLV-5

Cleaning Validation Philosophy, Strategies, and Methodology

Your Company's Logo **Your Company's Name**

5.1 Cleaning Validation Philosophy

Current cleaning procedures utilized at ABC Pharmaceutical Company have been structured to ensure that maintaining detailed cleaning methods in the Manufacturing areas and preventing contamination will not compromise the integrity of the product.

5.2 Cleaning Validation Strategies

5.2.1 General

Based on the selection of specific products for all production equipment, three consecutive lots are to be studied during a cleaning validation. All three lots must pass the acceptance criteria for chemical residue and microbial burden for the cleaning method to be validated.

Equipments in the Manufacturing and Filling areas are subjected to cleaning (manual and/or CIP/SIP (steam in place)) immediately following any production use in which they come into direct contact with the product.

The following factors were considered in the design of the cleaning validation program:

- To avoid the potential for localized contamination, selection of "hardest to clean" sample sites for the equipment and development of the respective cleaning procedure will be done.

5.2.2 Specific

Cleaning validation studies will be conducted for products/processes representing worst-case scenarios. Validation of the worst-case matrix ensures that the current cleaning practices at ABC Pharmaceutical Company are robust and

- Reduce the risk of cross-contamination
- Minimize the potential for product spoilage through microbial contamination
- Minimize the potential for adverse effects in consumers

Your Company's Logo **Your Company's Name**

The following criteria will be used to select the process and/or product over which the study shall be performed:

- Solubility of raw materials in the product, specifically the combination of least soluble product in water (the cleaning agent) and largest concentration to which the particular product occurs.
- Potency of the product (therapeutic dose).
- Toxicity of the active ingredient in the product, specifically the combination of most toxic ingredient and largest concentration to which the particular product occurs, as applicable.
- Most difficult product residue to clean, based on experience.
- Coverage of all equipment through each train. Equipment will be grouped based on elements of similar design/surface composition, if the same cleaning procedure is used for all sizes. Equipment that utilizes different cleaning techniques should be noted and rated accordingly.

5.3 New Products, Equipment, and Processes

The introduction of any new product, equipment, or process must proceed through ABC Pharmaceutical Company change control procedure No. QABC-001.

Before the introduction of any new product to Manufacturing or the Packaging department, an evaluation is to be made using the following criteria:

- Solubility of active materials in water
- Toxicity of the active material
- Potency of the product

In case of an active material that is already a worst-case designate, concentrations will be compared between the new products and existing products, and the product with the active material in higher concentration will be deemed the "worst case." A new cleaning validation study will be conducted if the new product has been deemed "worst case" by this investigation; otherwise, the existing cleaning validation study relevant to the particular worst-case product and equipment train will prevail.

Similarly, if a new cleaning procedure is introduced, which may impact the cleanliness of the process equipment (e.g., automated CIP procedures or new cleaning agents employed), it will undergo a new cleaning validation study for the relevant worst-case products.

New equipment addition in the production of any products that are not covered within the groupings listed in the CVMP will require a new cleaning validation study for the product deemed worst case on the relevant equipment train.

New products, processes, and equipments will be identified in subsequent revisions of this VMP.

Your Company's Logo **Your Company's Name**

5.4 Cleaning Validation Methodology

The cleaning validation program at ABC Pharmaceutical Company will be implemented in the following phases:

1. Planning (ABC Pharmaceutical Company CVMP development, including cleaning matrix development)
2. Analytical Method Development
3. Validation Protocol Development
4. Validation Execution (Sampling)
5. Validation Analytical Testing and Reporting
6. Ongoing Monitoring and Maintenance

CLV-6

Planning Phase

Your Company's Logo

Your Company's Name

6.1 Prevalidation Requirements

Prior to the initiation of the cleaning validation study, the following requirements should be met.

6.1.1 Equipment

Equipment qualification should be available prior to the initiation of the study on the relevant equipment. The design of the equipment along with the surface material and surface area of the product contact part should also be known.

6.1.2 Cleaning Procedures

Approved cleaning procedures should be available before the study starts.

6.1.3 Personnel Training

Personnel involved in the cleaning validation should be trained. Training records must be available for any training received.

6.2 Worst-Case Product Selection Matrix

The Product Equipment Grouping Matrix lists the products manufactured in the Manufacturing and Filling areas.

The selection of worst-case products is conducted in the following manner:

1. Worst-case products will be selected for each equipment train.
2. For each equipment train, worst-case product(s) will be selected such that
   a. A cleaning validation study would be performed for the bulk batch product containing the least soluble material.
   b. A cleaning validation study would be performed for the bulk batch product containing the most toxic and potent material, if this product differed from that chosen in part a above.

c. A cleaning validation study would be considered for every product deemed "hard to clean" by production staff following the production of bulk batches. The *difficult-to-clean* bulk batches are indicated in matrixes and include their rationale for inclusion in the cleaning validation program.
d. Wherever possible, the criteria in a, b, and c will be combined to select one worst-case product representing all scenarios.

3. The list of defined equipment trains is included in Matrix II.
4. Products manufactured on each train are indicated in Matrix III.
5. Solubility data for all active/excipient materials will be gathered and tabulated.
6. Toxicity data for all active materials will be gathered and tabulated.
7. Products will also be examined for raw material ingredients of high toxicity and potency.
8. Members of the production staff were also consulted for their experience in cleaning.

6.3 Analytical Development

Analytical methods will be developed if not available prior to initiating the cleaning validation study for all worst-case products (active ingredients) as designated in the Planning Phase.

The basic requirements are

- Ability to detect target substances at levels consistent with the acceptance criteria
- Ability to detect target substances in the presence of other materials that may also be present in the sample (selectivity)
- An analytical method that includes a calculation to convert the amount of residue detected in the sample to 100% if the recovery data generated indicate a recovery outside of an allowed range
- Stability of samples over time if the time interval between removal and testing of samples potentially affects sample integrity

6.4 Recovery

Definitive amounts of active drugs will be spiked onto the same surface as the equipment to be studied in the cleaning validation, so as to determine the recovery with swabs. Swabs are to be extracted and analyzed using an approved and validated method.

Your Company's Logo **Your Company's Name**

Recovery studies evaluate the quantitative recovery of chemical residue from both the surface to be sampled and the swab material used in sampling. All equipment surface types are to be included in the recovery study as different surfaces can exhibit different affinities for residues. Examples of different equipment surfaces are stainless steel, plastics, silicones, neoprene, glass, and so on.

6.5 Protocol Development

A cleaning validation protocol will be developed for each *worst-case product per equipment train* identified from the matrix incorporating the guidelines and requirements. These protocols will also be used to define specific sampling locations for each of the equipments included within the equipment train for the particular product under study.

The protocol must be prepared prior to the initiation of the study and must include all other documentation required to provide the following information.

- *Objective of the study*: The objective of the protocol should clearly refer to the cleaning procedure that is to be validated. If the study is employed to demonstrate the acceptability of the cleaning procedure for a group of products, the rationale for doing so will be detailed here.
- *Scope of the study*: The validation professional will evaluate the process and determine the residues (including cleaning agents) to be tested.
- *Listing of the process parameters to be verified*: This is particularly necessary when automated or semiautomated cleaning techniques are employed.
- *Sampling and inspection procedures*: Types of sampling methods, number of samplings, and sites of sampling will be described. Any particular requirements should also be stated, that is, for sterile sampling or sampling light-sensitive products. An equipment-sampling diagram should be referenced.
- *Personnel responsibilities during the study*: The designations and details of the responsibilities of personnel involved in the validation study will be included in this part.
- *Test methods to be used*: All the test methods used in the study will be indicated here.
- *Acceptance criteria*: The rationale for this criterion should be given along with a calculation step.
- *Change control*
- *Approval of protocol before the study*: Managers of the respective areas, including the validation manager and the director of Quality Assurance, will duly sign off the protocol before execution.

CLV-7

Execution Phase

Your Company's Logo

Your Company's Name

7.1 Visual Examination

After the cleaning, both product contact and nonproduct contact surfaces of the equipment are to be visually inspected for the presence of drug product traces. Verification of equipment cleanliness has to be done before sampling of product contact surfaces can commence. Surrounding areas (floor, walls, etc.) should also be visibly cleaned of product and detergent residue.

7.1.1 Sampling

Depending on the contamination or the residue that is being tested for and the analytical method used, it is very important to determine the type of sampling material to be used and its impact on the test results, as the material may interfere with the analysis of the samples.

It is also important to ensure that the solvent used for extraction purposes is satisfactory. The solvent must be nontoxic and is usually ethanol, water or an ethanol–water combination.

Several different sampling methods can be used, but the direct surface sampling method is preferred.

The validation officer of the company will execute the protocol.

Sample site selection will be based on areas that are deemed *hardest to clean*. Criteria include

- Equipment complexities (areas of different geometry that are likely to be difficult to clean)
- Areas of different materials of construction
- Ability to access and reproducibility of the sample

The number of sites to sample will be based on the above considerations as well as on the overall dimensions of the equipment. If there is an area that is deemed more "difficult to clean" during a cleaning validation, it will be included in that specific validation program.

7.1.2 Swab Sampling

To ensure that current equipment cleaning procedures are effective in reducing the residual concentrations of active ingredients to acceptable levels, swabs will be used to collect samples from production equipment after cleaning. These swabs will be used to determine both microbial and chemical contaminants.

Samples of the internal surfaces are then taken by moistening the swab with a suitable solvent, sampling a 5-cm^2 area (or the entire area if small), and then placing the swab in a test tube containing 10 mL of the solvent (specified for each active material from the analytical test method available in the laboratory or from pharmacopeias). For walls and plane surfaces, a minimum area of 5 cm^2 will be covered.

It is important to take a representative sample of the area, as the results will be calculated for the entire surface area at a later stage.

Swabbing will occur after the equipment has been cleaned and in accordance with SOPs. Swabbing has been deemed an advantageous method because it comes in direct contact with the sampling surface, allowing for the detection of substances that are not easily rinsed off or soluble.

Swab samples will be collected from maximum contact areas and areas that are difficult to clean. Both major and minor pieces of equipment, as well as different surfaces, will be assessed where possible (if applicable to the manufacturing process).

7.1.3 Rinse Sampling

It is important to have both kinds of sampling, that is, swabs and rinses. The inclusion of rinse water sampling ensures that contaminants that may not be attainable or that may have been missed through swab sampling/analysis are detected from the surface of the equipment. This sampling technique is especially advantageous when a CIP system is utilized.

Samples of machine rinses are collected in a 500-mL volumetric flask after final rinsing of the machine with purified water, as described in the individual equipment cleaning SOP. The residues in water may be determined by TOC, spectrophotometry, TLC, or conductivity comparison with purified water/water for injection or the HPLC method or any other suitable method described.

Details of samples taken by the validation team are recorded on a sampling sheet for ease of reference. This includes all the information required to ensure that the necessary samples are taken properly as well as any information required to calculate the results.

CLV-8

Analytical Testing and Reporting Phase

Your Company's Logo **Your Company's Name**

Before the cleaning validation can be started, companies must ensure that the analytical test methods, which are to be used for the cleaning validation, are completed and validated. The lack of a validated analytical method would result in the risk of repeating the entire cleaning validation after the method is validated.

This chapter deals with the development of the acceptance criteria of analytical tests and reports.

8.1 Acceptance Criteria

8.1.1 Limits Determination

The determination of cleaning limits and acceptance criteria is a crucial element of a good cleaning validation program. A limit is an actual numerical value and is one of the requirements of the acceptance criteria of a cleaning validation protocol. Limits and criteria should be

- Practical
- Verifiable
- Achievable
- Scientifically sound

The safety factor (SF) is a measure of risk that varies with dosage forms and routes of administration. It reduces the measurement of daily dose by a risk factor to ensure that safe levels are always attained. PDA Guideline Volume # 52 suggests the following SFs:

- Topical 1/10th–1/100th of a normal daily dose
- Oral dosage products: 1/100th–1/1000th of a normal daily dose
- Injection/ophthalmic products: 1/1000th–1/10,000th of a normal daily dose
- Research/investigational products: 10,000th–100,000th of a normal daily dose

CGMP and GLP limits are mentioned in the presentation.

The limits calculation criterion is based on the size and unit dose of the "next subsequent batch," that is, the next batch manufactured in the same equipment that is affected by any of the residues (i.e., an unclean piece of equipment) and is magnified accordingly, depending on batch size. The cleaning limits can therefore vary, depending on the batch size of the product manufactured subsequently. A worst-case scenario will be selected by combining the solubility, toxicity, potency, and batch size of the product.

8.1.2 Microbial Burden

The swab/rinse sampling of selected areas of the equipment train will be performed in order to determine the number of colony forming units (CFUs) present. The procedure used is listed in ABC Pharmaceutical Company's SOP No. ABC-111 Environmental Monitoring Program, with the upper limits at: there should not be any pathogenic bacteria detected.

If there is any growth observed, appropriate tests to identify the organism(s) are to be conducted.

8.1.3 Analytical Results Reporting

The QC lab analyst will perform the analysis on the swab and/or rinse samples. The results will be reported to the QA department.

The QA manager and the QC department manager will give final approval to the reviewed results by signing the final report. The director of the QA division will approve the final report.

8.1.4 Incident Investigation

In case of any results that do not meet the acceptance criteria, investigation will be carried out to determine the root cause as per site out of specification (OOS) investigation SOP. The validation officer together with a QA designate will conduct this investigation. All other team members will participate in this investigation as and when required. If necessary, changes should be recommended to prevent a reoccurrence.

The incident investigation should be a separate report detailing

- Cleaning validation protocol identification (name/date)
- Equipment identification
- Initiator and date
- Cleaning sample identification (e.g., swab, location of sample)
- Incident description
- Root-cause analysis
- Corrective actions recommended
- Assessment of effect on product

Your Company's Logo Your Company's Name

8.1.5 Reports

On completion of the requirements of the cleaning validation protocol, a report will be written summarizing the outcome of the cleaning validation.

A validation report is necessary to present the results and conclusions with the approval page duly signed off by corresponding signatories depicting the approval of validation study. The report will include the following:

- Summary of the procedures used to clean, sample, and test
- Physical and analytical test results as well as any excursions or deviations observed
- Conclusions regarding the acceptability of the results and the status of the procedures being validated
- Any recommendations based on the results obtained during the study, including revalidation practices if applicable
- Approval of conclusions
- Review of any protocol deviations that occurred
- Interim reports generated on a batch-by-batch basis until the cleaning validation study is completed (in cases where it is unlikely that further batches of the product will be manufactured for a period of time)
- An appropriate level of verification subsequent to validation

8.1.6 Monitoring

The conditions used during each cleaning validation study will be kept in control by

- Reviewing any changes made to the cleaning procedure
- Reviewing any changes made to equipment
- Supervisors training employees on the correct cleaning method and maintaining observation of technique after training is completed (see the company's SOP No. ABC-222 Employee Training Program)
- Completing cleaning records for traceability

8.1.7 Change Control/Revalidation

Any changes to the processing equipment in manufacturing, cleaning procedures, cleaning agent, product formulation, or the introduction of a new product will be documented and the effect on the clean state of the equipment will be determined through the change control process. The production manager, QC manager, and QA manager who decide whether revalidation is necessary must review the change.

CLV-9

Equipment Description

Your Company's Logo **Your Company's Name**

In this chapter, a detailed list of equipment used in ABC Pharmaceutical Company is presented in the tables below. These equipments are divided into categories for solid, liquid, and injectable manufacturing areas.

Equipment found in these areas must meet the specific acceptance criteria to be considered qualified/validated.

This would be the first step in identifying the worst-case product for cleaning validation. The basic idea would be to develop, based on the equipment and products list, the equipment train for each product type from different dosage forms. This practice will make the task of identifying the worst-case product much easier and simpler.

9.1 Solid Dosage Manufacturing

9.1.1 Equipment Description

Equipment Location/Room No.	Activity	Machine Name and Model
A-1	Line 1—tablets/capsules blistering	ABC Pac system, tablet hopper tablet channel
	Line 2—tablets/capsules blistering	ABC Pac system II, blistering machine
A-2	Alu-Alu blister	Striping machine
A-3	Tablet counting	Container-packing machine
A-4	Weighing booth 1	Scoops, spatula
A-5	Weighing booth 2	Scoops, spatula
A-6	Preparation room 1	Mixers
A-7	Preparation room 2	Solution preparation vessels
A-8	Granulation room 1	Granulator, fluid bed dryers
A-9	Granulation room 2	Granulator and vacuum dryer, weighing stations

Your Company's Logo **Your Company's Name**

Room No.	Activity	Machine Name	Model and Serial/ Asset No.
1	Blending	Tumbler blender 2000 L	Model of the machine
2	Tablet compression I	Tablet press with fully computerized in-process check master and dedusting system	Model of the machine
3	Bulk loading room I	Bin-emptying station	Model of the machine
	Tablet compression II	Tablet press with fully computerized in-process check master and dedusting system	
4	Bulk loading	Bin-emptying station	Model of the machine
	Tablet compression III	Tablet press with fully computerized in-process check master and dedusting system	
5	Bulk loading	Bin-emptying station	Model of the machine
6	Tablet compression IV	Tablet press with fully computerized in-process check master and dedusting system	Model of the machine
7	Bulk loading room IV	Bin-emptying station	Model of the machine
8	Tablet compression V	Fully computerized with in-process check master	Model of the machine
9	Bulk loading room V	Bin-emptying station	Model of the machine
	Capsules filling I	Capsule-filling machine	
10	Bulk loading room VI	Bin-emptying station	Model of the machine
	Capsules filling II	Capsule-filling machine	
11	Bulk loading room VII	Bin-emptying station	Model of the machine
12	Sugar coating	Sugar-coating pan with suspension Cota	Sugar cota 60–130 kg
13	Film coating I	Film-coating machine with cotab	Cota 1
14	Film coating II	Film-coating machine with cotab	Cota 2
15	Film coating III	Film-coating machine with cotab	Cota 3
15	Loading I	Tablet-transfer system	T-Mail
16	Loading II	Tablet-transfer system	Model of the machine
17	Loading III	Tablet-transfer system	Model of the machine
18	Powder filling	Powder for suspension filling	Model of the machine
19	Loading V	Bin-emptying station	Model of the machine
20	Washing area	Bin-washing station	Model of the machine
21	Powder bins	Powder bins 600 L	Model of the machine
		Powder bins 1000 L	Model of the machine
		Powder bins 2000 L	Model of the machine
22	Tablet bins	Tablet bins 300 L	Model of the machine
		Tablet bins 500 L	Model of the machine
23	Sieves		Model of the machine
24	Tablet deduster		Model of the machine
25	Piping/tubing/hoses		Model of the machine
26	Homogenizer		Model of the machine
27	Sorting machine		Model of the machine
28	Deblistering machine		Model of the machine

Your Company's Logo **Your Company's Name**

Room No.	Activity	Machine Name	Model and Serial/Asset No.
21	Powder filling	Powder-filling machine	Model of the machine
	Powder filling	Powder-capping machine	Model of the machine
22	Capsule filling	Capsule-filling machine	Model of the machine
23	Milling	AAA mill	Model of the machine
	Milling	AAA sifter	Model of the machine
24	Washing	Bin-weighing station	Model of the machine
	Blending	AAA tumbler	Model of the machine
	Blending	AAA bins	Model of the machine
25	Dispensing	Weighing cabinet (balance)	Model of the machine
26	Washing	Automatic washing station	Model of the machine

9.2 Sterile

9.2.1 Equipment Description (Injectables)

Room No.	Activity	Equipment's Description	Model and Serial/Asset No.
S1	Filling and closing	Filling and closing machine for syringes	Model of the machine
S2	Preparation	300 L manufacturing vessel	Model of the machine
	Preparation	300 L mobile vessel	Model of the machine
	Preparation	Mobile vessel	Model of the machine
	Preparation	Preparation reactor	Model of the machine
	Preparation	Formulation tank	Model of the machine
	Preparation	Mobile holding tank	Model of the machine
	Preparation	Formulation tank	Model of the machine
S3	Filling	Tank	Model of the machine
S4	Freeze drying	Freeze dryer	Model of the machine
S5	Filling and closing	Automatic vials filling and closing machine	Model of the machine
S6	Filling and closing	Ampoules filling and closing machine	Model of the machine
S6	Filtration	Filtration accessories, hoses	Model of the machine
	Dispensing	Material dispensing cabinet	Model of the machine
	Filtration	Filtration assembly	Model of the machine

Your Company's Logo Your Company's Name

9.3 Liquid Manufacturing

9.3.1 Equipment Description (Soft Product)

Vessel No.	Activity	Vessel's Description	Capacity/Make/Model
Raw Material Silos			
L1	Raw material storage	Sorbitol	XXX L/make XYZ company/model ABC
L2		Sorbitol	XXX L/make XYZ company/model ABC
L3		Propylene glycol	XXX L/make XYZ company/model ABC
L4		Propylene glycol	XXX L/make XYZ company/model ABC
L5		Glycerin	XXX L/make XYZ company/model ABC
L6		Glycerin	XXX L/make XYZ company/model ABC
L7		Syrup sugar vessel	XXX L/make XYZ company/model ABC
L8		Syrup sugar vessel	XXX L/make XYZ company/model ABC
L9		$Al(OH)_3$	XXX L/make XYZ company/model ABC
L10		$Al(OH)_3$	XXX L/make XYZ company/model ABC
Preparation Vessels			
L11	Preparation	Sugar solution	XXX L/make XYZ company/model ABC
L12		Gel dilution	XXX L/make XYZ company/model ABC
L13		Intermediate solution preparation	XXX L/make XYZ company/model ABC
		Mixer	XXX L/make XYZ company/model ABC
		SS bins	XXX L/make XYZ company/model ABC
Manufacturing Vessels			
M-02	Manufacturing	Syrup preparation	XXX L/make XYZ company/model ABC
M-03		Syrup preparation	XXX L/make XYZ company/model ABC
M-04		Syrup preparation	XXX L/make XYZ company/model ABC
M-05		Suspension preparation	XXX L/make XYZ company/model ABC
M-06		Suspension preparation	XXX L/make XYZ company/model ABC
M-07		Oral drops preparation	XXX L/make XYZ company/model ABC
M-08		Manufacturing vessel	XXX L/make XYZ company/model ABC
M-09		Melting vessel	XXX L/make XYZ company/model ABC
M-10		Sterile cream manufacturing machine	XXX L/make XYZ company/model ABC

Your Company's Logo

Your Company's Name

Vessel No.	Activity	Vessel's Description	Capacity (L)
Holding Tanks			
G-01	Syrup/suspension/ drops holding	Syrup storage vessel	7500
G-02		Syrup storage vessel	7500
G-03		Syrup storage vessel	7500
G-04		Syrup storage vessel	7500
G-05		Syrup storage vessel	7500
G-06		Syrup storage vessel	7500
G-07		Suspension storage vessel	5000
G-08		Suspension storage vessel	10,000
G-09		Suspension storage vessel	10,000
G-10		Oral drops storage vessel	2500
G-11		Oral drops storage vessel	2500

9.4 Filling Lines

9.4.1 Equipment Description (Soft Product)

Filling Lines	Description of Equipments		
Filling line 1	Filling tank	Hoses/tubing	Nozzle
Filling line 2	Filling tank	Hoses/tubing	Nozzle
Filling line 3	Filling tank	Hoses/tubing	Nozzle
Filling line 4	Filling tank	Hoses/tubing	Nozzle
Filling line 5	Filling tank	Hoses/tubing	Nozzle
Suppository filling line 6	Filling tank	Hoses/tubing	Nozzle
Cream/ointment filling line 7	Filling tank	Hoses/tubing	Nozzle
Sterile cream filling line	Filling tank	Hoses/tubing	Nozzle

CLV-10

Facility Description

Your Company's Logo

Your Company's Name

10.1 Solid Dosage Manufacturing

10.1.1 Facility Description

Room No.	Activity	Wall	Floor	Other
B1	Blister line 13	√	√	
B2	Tablet counting line 14	√	√	
	Weighing booth I	√	√	
	Weighing booth II	√	√	
B3	Preparation room I	√	√	
	Solution preparation	√	√	
	Preparation room II	√	√	
	Preparation room III	√	√	
B4	Granulation I	√	√	
	Granulation II	√	√	
	Blending I	√	√	
B5	Blending II	√	√	
B6	Lifting	√	√	
	Tablet compression I	√	√	
	Bulk loading room I	√	√	
B7	Tablet compression II	√	√	
B8	Bulk loading room II	√	√	
	Tablet compression III	√	√	
B9	Bulk loading room III	√	√	
	Tablet compression IV	√	√	
	Bulk loading room IV	√	√	
B9	Tablet compression V	√	√	
B10	Bulk loading room V	√	√	
	Capsules filling I	√	√	
	Bulk loading room VI	√	√	

continued

Your Company's Logo **Your Company's Name**

Room No.	Activity	Wall	Floor	Other
B11	Capsules filling II	√	√	
	Bulk loading room VII	√	√	
B12	Sugar coating	√	√	
	Film coating I	√	√	
B13	Film coating II	√	√	
B14	Film coating III	√	√	
B15	Loading I	√	√	
B16	Loading II	√	√	
B17	Loading III	√	√	
B18	Powder filling line 15			
B19	Loading IV	√	√	
—	Powder bins	√	√	
—	Tablet bins	√	√	
		√	√	

CLV-11

Utilities Description: DIW, WFI, Steam, and Compressed Air

Your Company's Logo **Your Company's Name**

11.1 Utilities Description

The major utilities involved in the routine operation of a plant, which are used to a great extent in the cleaning of products, are as follows.

11.1.1 Water System

ABC Pharmaceutical Company manufactures two levels of water quality: water for injection (WFI) for sterile products and purified water for other dosage forms.

City water is supplied from a municipality source and enters the ABC Pharmaceutical Company building. After passing through a backflow preventer, it is diverted to general plant use or to the purified water pretreatment system, which includes a reverse osmosis (RO) system. This system supplies purified deionized water (DIW) to the pure steam generator, the ampoule/vial washer, cleaning use points, and the distillation unit used to produce WFI.

11.1.2 WFI System

The condensate of the heated vapor (free distillate) is collected in the condenser, where the vapor is cooled and condensed by incoming cooling water. WFI is collected in the main storage tank (6000-L capacity) from where two loops, one for the CIP of the freeze dryer and the other for distribution in building C, start.

Temperature indicators are used to monitor the temperature continuously. The temperature requirement is >85°C for the WFI tank and >80°C for the water distribution system. Conductivity and temperature at the return of the loop are monitored and registered on control panels. Sampling points are available near each main point of use.

Weekly chemical and physical monitoring of WFI from commodity washing and solution preparation is performed. The same two points are also used for daily microbiological monitoring along with the parenteral area WFI inlet.

11.1.3 Purified Water System

The GMP design of the water treatment plant aims to produce purified water from city water. The purified water quality complies with USP pharmacopeia.

The system consists of

1. Chlorination dosing set
2. Heat exchanger for raw water-cooling
3. Sand filter
4. Carbon filter
5. Antiscalant dosing set
6. 5-µm filter
7. RO station
8. Potable water tank
9. Deionizer
10. UV sterilizer
11. Purified water tank

Purified water circulates in a stainless steel loop supplying purified water to the required use points. The water treatment plant is fully automatic and is controlled through a control room in the utilities area.

11.1.4 Process Chilled Water System

Chilled water is an important utility used for cooling purposes.

11.1.5 Steam System

Clean steam is used for all equipment, which comes into contact with containers, solution, or closures prior to product assembly. A generator fed by DIW produces pure steam. The steam generator is located on the first floor of the main building of ABC Pharmaceutical Company, from where the loop starts to different use points. Steam traps are installed to collect condensate when necessary. The quality of pure steam condensate is the same as established for WFI, USP. The quality of pure steam is monitored through a quality analyzer system that measures the conductivity of condensed pure steam.

Industrial steam is produced by two boilers, each with a capacity of 5000 kg/h. The system is fully automatic with a control and monitoring system. The steam is used for

- Heating during product processing
- Sanitization of the DI loop
- Sterilization of $Al(OH)_3$ vessels

11.1.6 Compressed Air

Oil-free compressed air is produced in rotary screw compressors. It is stored in a stainless steel receiver and then passes through a 1-µm filter for particle removal and through two

air dryers to ensure complete removal of moisture traces. It is delivered to the plant via a stainless steel loop that supplies all use points and is equipped with a filter and regulator.

Use points are defined to be critical, where compressed air quality is considered of medical grade, USP.

i. Vials-washing machine
ii. Sterilization autoclave
iii. Liquid-filling lines for bottles air blowing

11.1.7 Compressed Air (Solid and Liquid Products)

Oil-free compressed air is produced in two identical rotary screw compressors (model and make), each with a capacity of 15 m^3/min. Compressed air is stored in a stainless steel 316-L receiver (4-m^3 capacity) and then passes through a 1-µm filter for particle removal and through two air dryers to ensure complete removal of moisture traces.

The oil-free compressed air is delivered to the plant via a stainless steel 316-L loop that supplies all use points and has a filter and a regulator.

The system is monitored through a remote monitoring system (model and make) that senses the operation of the compressors and displays this in the control room.

11.1.8 Nitrogen System

Nitrogen is used for

- Purging during product preparation
- Purging during filtering of oxygen-sensitive products
- Vacuum break after powder transfer
- Weighing of oxygen-sensitive active materials

CLV-12

Utilities Monitoring and Microbiological Control

Your Company's Logo **Your Company's Name**

The following are the utilities monitoring and microbiological control procedures:

1. ABC-100: microbiological monitoring of water
2. ABC-200: microbiological environmental monitoring of clean room and other control environment
3. ABC-300: monitoring of microbiological quality of air and surface cleaning for tablet manufacturing area
4. ABC-400: microbiological monitoring of soft manufacturing plant
5. ABC-500: chemical and physical monitoring of DIW and WFI in ABC Pharmaceutical Company tablets and liquids plants

CLV-13

Equipment Cleaning Materials/Detergent Description

Your Company's Logo

Your Company's Name

13.1 Solid Dosage Plant

No.	Name	Chemical Nature
1	P3-cosa FOAM 40	Clear colorless liquid—density: 0.02–1.06; pH: 6.4–7.5. At 20°C, miscible with water in any proportion
2	White spirit	
3	Phosphoric acid	Phosphoric acid 85%
4	Lux liquid soap	Normal soap
5	Alcohol	95%
6	Solvitol	Green viscous liquid—pH: 7–8; specific gravity: 1.021
7	Clorax	Sodium hypochlorite: minimum 6%
8	Radol	
9	DIW	

13.2 Sterile Plant

No.	Name	Chemical Nature
1	White spirit	
2	Liquid soap	Normal soap
3	Alcohol	95%
4	DIW	

Your Company's Logo

Your Company's Name

13.3 Antibiotic Plant

No.	Name	Chemical Nature
1	Ethyl alcohol	C_2H_5OH
2	Propyl alcohol	C_3H_7OH
3	Tego 2000	Clear colorless to pale yellow liquid of pH 8.0
4	WFI	Water for injection (H_2O)

13.4 Liquid Dosage Plant

No.	Name	Chemical Nature
1	Solvitol	Green viscous liquid—pH: 7–8; specific gravity: 1.021
2	Caustic soda	NaOH
3	Hydrochloric acid	HCl
4	Phosphoric acid	$H_2(PO_4)_2$
5	Alcohol	C_2H_5OH
6	DIW	Deionized water (H_2O)

CLV-14

Microbiological Cleaning of Equipment Surface

Your Company's Logo **Your Company's Name**

The following are procedures for microbiological monitoring

S. No.	Description	SOP No.
1	Monitoring of microbiological quality of air and surface cleaning for the solid dosage plant	ABC-001
2	Water sampling technique	ABC-002
3	Monitoring of personnel hygiene	ABC-003
4	Water microbiological analysis	ABC-004
5	Microbiological environmental monitoring of clean room and other controlled environments facility and personnel	ABC-005
6	Chemical and physical monitoring of DIW and WFI in the solid dosage, liquid dosage, antibiotic, and sterile plants of ABC Pharmaceutical Company	ABC-006
7	Microbiological and chemical monitoring of nitrogen gas used in the antibiotic plant	ABC-007
8	Microbiological monitoring of the soft manufacturing plant	ABC-008
9	Sterile swab preparation	ABC-009
10	Microbiological monitoring of water	ABC-010

CLV-15

Solubility of Active Materials in Water

In this section, the solubilities of over 200 active pharmaceutical ingredients (APIs) are presented. The matrix shows the extent of solubility of the most commonly used APIs in the manufacture of medicines. Again, the purpose of this matrix is to help in the selection of worst-case products, containing these APIs for cleaning validation, based on their solubility in water or alcohol.

Active Ingredients	Solubility in Water
Activated attapulgite	Insoluble in water
Amphotericin	Practically insoluble in water, soluble in alcohol
Acyclovir	Soluble in water
Acebutolol hydrochloride	Freely soluble in water and in alcohol
Acetazolamide	Very slightly soluble in water, slightly soluble in alcohol
Albendazole	Insoluble in water and in alcohol
Aluminum hydroxide	Practically insoluble in water
Alprostadil	Practically insoluble in water, freely soluble in alcohol
Alprenolol hydrochloride	Very soluble in water, freely soluble in alcohol
Amantadine hydrochloride	Freely soluble in water and in alcohol
Amiodarone	Very slightly soluble in water
Ammonium chloride	Freely soluble in water
Amoxicillin	Slightly soluble in water
Ampicillin trihydrate	Slightly soluble in water, practically soluble in alcohol
Amikacin sulfate	Freely soluble in water
Aminophylline	Freely soluble in water
Aspirin	Insoluble in water, freely soluble in alcohol
Astemizole	Practically insoluble in water
Atropine sulfate	Very soluble in water
Atenolol	Sparingly soluble in water, soluble in ethanol
Azithromycin dihydrate	Practically insoluble in water, freely soluble in ethanol
Betamethasone valerate	Practically insoluble in water, soluble in alcohol
Bacitracin USP	Freely soluble in water, soluble in alcohol
Bacampicillin hydrochloride	Soluble in water
Bisacodyl	Insoluble in water, sparingly soluble in alcohol
Beclomethasone dipropionate	Very slightly soluble in water, freely soluble in alcohol
Betaxolol hydrochloride	Very soluble in water, freely soluble in alcohol
Bezafibrate	Practically insoluble in water, sparingly soluble in methanol
Benzalkonium chloride	Very soluble in water and in alcohol
Benzocaine	Very slightly soluble in water
Bifonazole	Practically insoluble in water
Bromocriptine mesylate	Practically insoluble in water

continued

Active Ingredients	Solubility in Water
Budesonide	Practically insoluble in water, sparingly soluble in alcohol
Buprenorphine hydrochloride	Sparingly soluble in water
Bufexamac	Practically insoluble in water
Bupivacaine hydrochloride	Soluble in water, freely soluble in alcohol
Calcium pantothenate	Insoluble in water
Caffeine	Freely soluble in boiling water
Carbamazepine	Very slightly soluble in water
Captopril	Freely soluble in water and in methanol
Carbidopa	Slightly soluble in water, very slightly soluble in alcohol
Carbachol	Very soluble in water, sparingly soluble in alcohol
Cetylpyridinium chloride	Very soluble in water
Calcitriol	Practically insoluble in water, freely soluble in alcohol
Calcium ascorbate	Freely soluble in water, practically insoluble in alcohol
Cinnarizine theophyllinate	Practically insoluble in water, freely soluble in CH_2Cl_2
Clobetasol propionate	Practically insoluble in water, sparingly soluble in ethanol
Cephalexin monohydrate	Slightly soluble in water, practically insoluble in alcohol
Cefaclor monohydrate	Soluble in water, insoluble in methanol
Cefixime	Slightly soluble in water
Cefazolin sodium	Freely soluble in water, very slightly soluble in alcohol
Ceftazidime	Slightly soluble in water
Cefuroxime axetil	Slightly soluble in water, soluble in methanol
Cefotaxime	Freely soluble in water
Ceftriaxone	Freely soluble in water, sparingly soluble in methanol
Cetirizine HCl	Freely soluble in water
Cephradine	Sparingly soluble in water
Chlorpheniramine maleate	Freely soluble in water
Chlorambucil	Practically insoluble in water, freely soluble in ethanol
Chloramphenicol	Slightly soluble in water, freely soluble in alcohol
Chlorcyclizine hydrochloride	Freely soluble in water, soluble in alcohol
Chlorhexidine	Miscible in water, soluble in alcohol
Chlorpromazine	Practically insoluble in water, freely soluble in ethanol
Ciclopirox	Slightly soluble in water, freely soluble in ethanol
Cimetidine	Slightly soluble in water, soluble in alcohol
Ciprofloxacin	Sparingly soluble in water, slightly soluble in alcohol
Clarithromycin	Practically insoluble in water, slightly soluble in dehydrated alcohol
Clavulanate potassium	Freely soluble in water, soluble in methanol
Clobutinol HCl	Freely soluble in water and in alcohol
Codeine phosphate	Freely soluble in water, soluble in ethanol
Colchicine	Very soluble in water
Cloxacillin sodium	Freely soluble in water and in methanol
Cyanocobalamin	Sparingly soluble in water and in alcohol
Cyclosporine	Practically insoluble in water, soluble in methanol
Dextromethorphan HBr	Sparingly soluble in water
Diphenhydramine HCl	Very soluble in water, freely soluble in alcohol
Diflunisal	Practically insoluble in water, soluble in alcohol
Diclofenac diethylamine	Sparingly soluble in water, freely soluble in methanol
Diethycarbamazine citrate	Very soluble in water, soluble in alcohol

Active Ingredients	Solubility in Water
Dexpanthenol	Freely soluble in water and in alcohol
Diazepam	Very slightly soluble in water, soluble in alcohol
Dimenhydrinate	Slightly soluble in water, freely soluble in alcohol
Diphenoxylate HCl	Sparingly soluble in water
Doxycycline hyclate	Soluble in water, slightly soluble in alcohol
Ephedrine HCl	Freely soluble in water, soluble in ethanol
Enalapril maleate	Soluble in water
Erythromycin	Practically insoluble in water, soluble in methanol
Etodolac	Practically insoluble in water, freely soluble in ethanol
Famotidine	Very slightly soluble in water, slightly soluble in methanol
Felodipine	Practically insoluble in water, freely soluble in ethanol
Fenoprofen calcium	Slightly soluble in water, soluble in methanol
Fluxetine HCl	Sparingly soluble in water, freely soluble in alcohol
Fluticasone propionate	Practically insoluble in water, slightly soluble in ethanol
Folic acid	Practically insoluble in water
Fluvoxamine maleate	Sparingly soluble in water, very soluble in methanol
Flutamide	Practically soluble in water, freely soluble in alcohol
Fusidic acid	Practically insoluble in water, freely soluble in alcohol
Flunitrazepam	Practically insoluble in water, slightly soluble in alcohol
Flutamide	Practically insoluble in water, freely soluble in alcohol
Fluvoxamine maleate	Sparingly soluble in water
Ferrous sulfate (dried)	Freely soluble in water, very soluble in boiling water
Ferrous fumarate	Slightly soluble in water, very slightly soluble in alcohol
Furosemide	Practically insoluble in water, sparingly soluble in alcohol
Gemfibrozil	Practically insoluble in water, freely soluble in methanol
Ginseng	Freely soluble in water
Glibenclamide	Insoluble in water, slightly soluble in alcohol
Gliclazide	Practically insoluble in water, slightly soluble in alcohol
Glycerin	Soluble in water and in alcohol
Glyceryl guaiacolate	Freely soluble in water
Gramicidin	Insoluble in water
Heparin calcium	Freely soluble in water
Hydrocortisone	Insoluble in water, slightly soluble in alcohol
Hyoscine-*N*-butyl bromide	Freely soluble in water, sparingly soluble in ethanol
Ibuprofen	Practically insoluble in water
Indapamide	Insoluble in water, soluble in alcohol
Indomethacin	Practically insoluble in water, sparingly soluble in alcohol
Kaopectate	Insoluble in water
Ketotifen fumarate	Slightly soluble in water, sparingly soluble in methanol
Ketoconazole	Practically insoluble in water, soluble in methanol
Lacidipine	Practically insoluble in water, sparingly soluble in ethanol
Lomefloxacin HCl	Slightly soluble in water
Loratadine	Insoluble in water, soluble in methanol
Levofloxacin	Levofloxacin
Lidocaine HCl	Very soluble in water, freely soluble in alcohol
Magnesium aluminum silicate	Insoluble in water and in alcohol

continued

Active Ingredients	Solubility in Water
Magnesium hydroxide	Practically insoluble in water
Miconazole nitrate	Slightly soluble in water
Mebendazole	Practically insoluble in water
Menthol	Insoluble in water
Metronidazole	Sparingly soluble in water and in alcohol
Metoclopramide HCl	Very soluble in water, freely soluble in ethanol
Metformin HCl	Freely soluble in water, slightly soluble in alcohol
Nifedipine	Practically insoluble in water
Nicotinamide	Freely soluble in water
Norfloxacin	Slightly soluble in water
Nystatin topical	Insoluble in water
Neomycin sulfate	Freely soluble in water
Omeprazole	Freely soluble in water and in alcohol
Orphenadrine citrate	Sparingly soluble in water, slightly soluble in ethanol
Orciprenaline sulfate	Freely soluble in water and in alcohol
Orphenadrine hydrochloride	Freely soluble in water and in alcohol
Oxazepam	Practically insoluble in water, slightly soluble in alcohol
Oxybuprocaine HCl	Very soluble in water, freely soluble in alcohol
Oxymetazoline HCl	Freely soluble in water and in ethanol
Oxytetracycline	Freely soluble in water, sparingly soluble in alcohol
Paracetamol	Freely soluble in alcohol, soluble in boiling water
Papaverine hydrochloride	Sparingly soluble in water, slightly soluble in alcohol
Paroxetine HCl hemihydrate	Slightly soluble in water, freely soluble in methanol
Penicillamine	Freely soluble in water, slightly soluble in alcohol
Pentoxifylline	Soluble in water
Phenobarbital sodium	Freely soluble in water, soluble in alcohol
Phenylephrine HCl	Freely soluble in water
Phenylalanine	Sparingly soluble in water, very slightly soluble in alcohol
Piperazine citrate	Freely soluble in water, practically insoluble in alcohol
Propranolol HCl	Soluble in water
Prazosin hydrochloride	Very slightly soluble in water, slightly soluble in alcohol
Prednisolone	Very slightly soluble in water, Soluble in methanol
Promethazine HCl	Very soluble in water, freely soluble in alcohol
Procaine hydrochloride	Very soluble in water, soluble in alcohol
Proxyphylline	Very soluble in water, soluble in alcohol
Pheniramine maleate	Very soluble in water, freely soluble in alcohol
Pseudoephedrine HCl	Very soluble in water
Ranitidine HCl	Very soluble in water, moderately soluble in alcohol
Recombinant human erythropoietin	Sparingly soluble in water
Resorcinol	Very soluble in water and in alcohol
Rifampicin	Slightly soluble in water, soluble in methanol
Risperidone	Practically insoluble in water, sparingly soluble in alcohol
Salbutamol sulfate	Freely soluble in water
Salicylamide	Slightly soluble in water
Salicylic acid	Slightly soluble in water, freely soluble in alcohol
Sertaconazole nitrate	Practically insoluble in water, soluble in methanol
Silver sulfadiazine	Insoluble in water and in alcohol

Active Ingredients	Solubility in Water
Simvastatine sodium	Practically insoluble in water, freely soluble in methanol
Sodium alendronate	Soluble in water, very slightly soluble in methanol
Sodium citrate	Freely soluble in water
Sodium valproate	Very soluble in water, slightly to freely soluble in water
Sodium iodide	Very soluble in water, freely soluble in alcohol
Somatostatin	Freely soluble in water
Simethicone	Practically insoluble in water
Sucralfate	Insoluble in water
Succinylsulfathiazole	Very slightly soluble in water, slightly soluble in alcohol
Tamoxifene citrate	Very slightly soluble in water, soluble in methanol
Tetracycline HCl	Soluble in water
Theophylline	Slightly soluble in water, sparingly soluble in alcohol
Tribenoside	Very soluble in water and in alcohol
Triamcinolone acetonide	Insoluble in water
Triprolidine HCl	Soluble in water and in alcohol
Trimethoprim	Very slightly soluble in water, slightly soluble in alcohol
Tyrothricin	Practically insoluble in water, soluble in alcohol
Xylometazoline	Soluble in water
Vancomycin HCl	Freely soluble in water
Verapamil hydrochloride	Soluble in water, freely soluble in methanol
Vitamin A	Insoluble in water
Vitamin D	Insoluble in water
Vitamin C	Freely soluble in water
Vitamin B_1	Sparingly soluble in water
Vitamin B_2	Soluble in water
Vitamin B_6	Freely soluble in water
Vitamin B_{12}	Sparingly soluble in water
Xylometazoline hydrochloride	Freely soluble in water, alcohol, and methanol
Zinc oxide	Insoluble in water

Solubility Key	Solubility Scale in Numbers
Very soluble in water	1
Freely soluble in water	2
Soluble in water	3
Sparingly soluble in water	4
Slightly soluble in water	5
Very slightly soluble in water	6
Practically insoluble in water or insoluble	7

CLV-16

Toxicity of Active Materials

Your Company's Logo **Your Company's Name**

In the preceding chapter, solubilities of the APIs were presented. Likewise, the toxicities of the same active materials are shown in the matrix below. Toxicity was taken from the material safety data sheets of the respective materials.

Active Ingredients	Toxicity
Activated attapulgite	Nontoxic
Amphotericin	LD_{50} 88.0 g/kg intraperitoneal mouse
Acyclovir	LD_{50} 20.0 g/kg oral rat; LD_{50} 10.0 g/kg oral mouse
Acebutolol hydrochloride	LD_{50} 6620.0 g/kg oral rat
Acetazolamide	LD_{50} 4300 mg/kg oral mouse
Albendazole	LD_{50} 2400.0 mg/kg oral rat
Aluminum hydroxide	LD_{50} 9500 mg/kg oral rat
Alprostadil	LD_{50} 186.0 mg/kg oral mouse
Alprenolol hydrochloride	LD_{50} 590.0 mg/kg oral rat
Amantadine hydrochloride	LD_{50} 700.0 mg/kg oral mouse
Ambroxol hydrochloride	LD_{50} 13,400.0 mg/kg oral rat
Amiodarone	LD_{50} 2600.0 mg/kg oral rat
Ammonium chloride	LD_{50} 1650.0 mg/kg oral rat
Amoxicillin	LD_{50} 15.0 g/kg oral rat; LD_{50} 25 g/kg oral mouse
Ampicillin trihydrate	LD_{50} 10,000 mg/kg oral rat
Amikacin sulfate	LD_{50} >6000 mg/kg oral mouse
Aminophylline	LD_{50} 243 mg/kg oral rat
Aspirin	LD_{50} 200 mg/kg oral rat
Astemizole	LD_{50} 2560.0 g/kg oral rat; LD_{50} 2560.0 g/kg oral mouse
Atropine sulfate	LD_{50} 600 mg/kg oral rat
Atenolol	LD_{50} 2000.0 mg/kg oral mouse/rat
Azithromycin dihydrate	LD_{50} 2.0 g/kg oral rat; LD_{50} 3.0 g/kg oral mouse
Betamethasone valerate	LD_{50} 3.0 g/kg oral rat; LD_{50} 4067 mg/kg oral mouse
Bacitracin USP	LD_{50} 3750.0 mg/kg oral mouse
Bacampicillin hydrochloride	LD_{50} 10,000.0 g/kg oral rat
Bisacodyl	LD_{50} 4320 mg/kg oral rat
Beclomethasone dipropionate	LD_{50} 3750.0 mg/kg oral rat

continued

Your Company's Logo **Your Company's Name**

Active Ingredients	Toxicity
Betaxolol hydrochloride	LD_{50} 998.0 mg/kg oral rat; LD_{50} 48.0 mg/kg oral mouse
Bezafibrate	LD_{50} 1082.0 mg/kg oral rat
Benzocaine	LD_{50} 1150.0 mg/kg oral rabbit
Benzalkonium chloride	LD_{50} 240.0 mg/kg oral rat
Bromhexine HCl	LD_{50} 1226 mg/kg oral rat
Bifonazole	LD_{50} 1463.0 mg/kg oral rat; LD_{50} 2629.0 mg/kg oral mouse
Budesonide	LD_{50} 4750.0 mg/kg oral mouse
Buprenorphine hydrochloride	LD_{50} 1000 mg/kg oral rat
Bufexamac	LD_{50} 3370.0 mg/kg oral rat; LD_{50} 8000.0 mg/kg oral mouse
Bupivacaine hydrochloride	LD_{50} 43 mg/kg subcutaneous rat
Calcium pantothenate	LD_{50} 10 g/kg oral rat
Caffeine	LD_{50} 127 mg/kg oral mouse
Carbamazepine	LD_{50} 1957 mg/kg oral rat
Carbinoxamine	LD_{50} 162 mg/kg oral mouse
Carbachol	LD_{50} 40.0 mg/kg oral rat; LD_{50} 15.0 mg/kg oral mouse
Captopril	LD_{50} 4245 mg/kg oral rat
Carbidopa	LD_{50} 1750 mg/kg oral mouse
Cetylpyridinium chloride	LD_{50} 200.0 mg/kg oral rat; LD_{50} 108.0 mg/kg oral mouse
Calcitriol	LD_{50} 0.62 mg/kg oral rat
Calcium ascorbate	LD_{50} 14,500.0 mg/kg oral rat; LD_{50} 1600.0 mg/kg oral mouse
Cinnarizine theophyllinate	LD_{50} 6500.0 g/kg oral rat; LD_{50} 4500.0 mg/kg oral mouse
Clobetasol propionate	LD_{50} 3.0 g/kg oral rat; LD_{50} 3.0 mg/kg oral mouse
Cephalexin monohydrate	LD_{50} 1495 mg/kg oral mouse
Cefaclor monohydrate	LD_{50} >20,000 g/kg oral rat
Cefixime	Nontoxic
Cefazolin sodium	LD_{50} 11,000.00 mg/kg oral rat
Ceftazidime	LD_{50} >20,000 mg/kg oral rat
Cefuroxime axetil	LD_{50} 5000 mg/kg oral rat
Cefotaxime	LD_{50} 20,000.00 mg/kg oral rat
Ceftriaxone	LD_{50}10.0 g/kg oral rat and oral mouse
Cetirizine HCl	LD_{50} 703.0 mg/kg oral rat
Cephradine	LD_{50} 5000 mg/kg oral mouse
Chlorpheniramine maleate	LD_{50} 130 mg/kg oral mouse; LD_{50} 300 mg/kg oral rat
Chlorambucil	LD_{50} 80 mg/kg oral mouse; LD_{50} 76 mg/kg oral rat
Chloramphenicol	LD_{50} 2500 mg/kg oral rat; LD_{50} 1500.0 mg/kg oral mouse
Chlorcyclizine hydrochloride	LD_{50} 300 mg/kg oral mouse
Chlorhexidine	LD_{50} 9200 µL/kg oral rat
Chlorpromazine	LD_{50} 145.0 mg/kg oral rat; LD_{50} 135.0 mg/kg oral mouse
Ciclopirox	LD_{50} 2350 mg/kg oral rat
Cimetidine	LD_{50} 5000 mg/kg oral rat
Cincochain HCl	LD_{50} 42 mg/kg oral bird
Ciprofloxacin	LD_{50} 5000 mg/kg oral rat; LD_{50} 5000 mg/kg oral mouse

Your Company's Logo **Your Company's Name**

Active Ingredients	Toxicity
Clarithromycin	LD_{50} 2700 mg/kg oral rat
Clavulanate potassium	LD_{50} 5000 mg/kg oral rat
Clobutinol HCl	LD_{50} 802 mg/kg oral rat
Codeine phosphate	LD_{50} 85 mg/kg oral rat
Colchicine	LD_{50} 5886 µg/kg oral mouse
Cloxacillin sodium	LD_{50} 5000 mg/kg oral rat
Cyanocobalamin	LD_{50} 2 g/kg oral mouse
Cyclosporine	LD_{50} 15,800 mg/kg oral rabbit
Dextromethorphan HBr	LD_{50} 350 mg/kg oral rat
Diphenhydramine HCl	LD_{50} 500 mg/kg oral rat
Diclofenac sodium	LD_{50} 390 mg/kg oral mouse; LD_{50} 150 mg/kg oral rat
Diflunisal	LD_{50} 392 mg/kg oral mouse; LD_{50} 439 mg/kg oral rat
Diethylcarbamazine citrate	LD_{50} 660 mg/kg oral mouse; LD_{50} 1400 mg/kg oral rat
Dexpanthenol	LD_{50} 15,000 mg/kg oral mouse
Diazepam	LD_{50} 48 mg/kg oral mouse
Dimenhydrinate	LD_{50} 681 mg/kg oral rat
Diphenoxylate HCl	LD_{50} 221 mg/kg oral rat
Doxycycline hyclate	LD_{50} 1900.0 g/kg oral mouse
Ephedrine HCl	LD_{50} 710 mg/kg oral rat
Enalapril maleate	LD_{50} 2973 mg/kg oral rat
Erythromycin	LD_{50} 10.0 g/kg oral mouse
Etodolac	LD_{50} 95 mg/kg oral rat
Famotidine	LD_{50} 4049 mg/kg oral rat
Felodipine	LD_{50} 1050 mg/kg oral rat
Fenoprofen calcium	LD_{50} 439 mg/kg oral mouse; LD_{50} 415 mg/kg oral rat
Fluxetine HCl	LD_{50} 452 mg/kg oral rat
Fluticasone propionate	LD_{50} 2000 mg/kg oral rat
Fluvoxamine maleate	LD_{50} 1100.0 mg/kg oral mouse
Flutamide	LD_{50} 787 mg/kg oral rat
Folic acid	LD_{50} 8000 mg/kg oral rat
Fusidic acid	LD_{50} 975.0 mg/kg oral mouse
Flunitrazepam	LD_{50} 415 mg/ kg oral rat
Flutamide	LD_{50} 787 mg/kg oral rat
Fluvoxamine maleate	LD_{50} 1100.0 mg/kg oral mouse
Ferrous sulfate (dried)	LD_{50} 1520 mg/kg oral mouse
Ferrous fumarate	LD_{50} 3850 mg/kg oral rat
Furosemide	LD_{50} 2600 mg/kg oral rat
Gemfibrozil	LD_{50} 1414 mg/kg oral rat
Ginseng	LD_{50} 750 mg/kg oral rat
Glibenclamide	LD_{50} >20,000 mg/kg oral rat
Gliclazide	LD_{50} 3000 mg/kg oral rat
Glycerin	LD_{50} 17 g/kg oral rat

continued

Your Company's Logo **Your Company's Name**

Active Ingredients	Toxicity
Glyceryl guaiacolate	LD_{50} 12600 mg/kg oral rat
Gramicidin	LD_{50} 1000 mg/kg oral mouse
Heparin calcium	LD_{50} >200 KU/kg oral rat; LD_{50} >400 KU/kg oral mouse
Hydrocortisone	LD_{50} 150 mg/kg oral rat
Hyoscine-*N*-butyl bromide	LD_{50} 1170 mg/kg oral mouse; LD_{50} 1040 mg/kg oral rat
Ibuprofen	LD_{50} 636 mg/kg oral rat; LD_{50} 740 mg/kg oral mouse
Indapamide	LD_{50} >3000 mg/kg oral rat
Indomethacin	LD_{50} 2.42 mg/kg oral rat
Kaopectate	LD_{50} >5000 mg/kg oral rat
Ketotifen fumarate	LD_{50} 360 mg/kg oral rat; LD_{50} 585 mg/kg oral mouse
Ketoconazole	LD_{50} 166.0 mg/kg oral rat; LD_{50} 618 mg/kg oral mouse
Lamotrigine	LD_{50} 185 mg/kg oral rat; LD_{50} 269 mg/kg oral mouse
Lomefloxacin HCl	LD_{50} 1556 mg/kg oral rat
Loratadine	LD_{50} >5000 mg/kg oral rat
Levofloxacin	LD_{50} 35,900 mg/kg oral rat; LD_{50} 3366 mg/kg oral mouse
Lidocaine HCl	LD_{50} 292 mg/kg oral mouse
Magnesium aluminum silicate	LD_{50} 16,000 mg/kg oral rat
Magnesium hydroxide	LD_{50} 8500 mg/kg oral rat
Miconazole nitrate	LD_{50} 920 mg/kg oral rat; LD_{50} 578 mg/kg oral mouse
Mebendazole	LD_{50} 714 mg/kg oral rat; LD_{50} 620 mg/kg oral mouse
Menthol	LD_{50} 3300 mg/kg oral rat
Metronidazole	LD_{50} 3000 mg/kg oral rat
Metoclopramide HCl	LD_{50} 280 mg/kg oral mouse
Metformin HCl	LD_{50} 4000 mg/kg oral rat
Nifedipine	LD_{50} 1022 mg/kg oral rat
Nicotinamide	LD_{50} 3500 mg/kg oral rat
Norfloxacin	LD_{50} >4000 mg/kg oral rat
Nystatin topical	LD_{50} 10,000 mg/kg oral rat; LD_{50} 8000 mg/kg oral mouse
Neomycin sulfate	LD_{50} 8.0 g/kg oral mouse
Omeprazole	LD_{50} 2210 mg/kg oral rat; LD_{50} 4.0 g/kg oral mouse
Orphenadrine citrate	LD_{50} 150 mg/kg oral mouse
Orciprenaline sulfate	LD_{50} 5538 mg/kg oral rat
Orphenadrine hydrochloride	LD_{50} 255 mg/kg oral rat
Oxazepam	LD_{50} >8000 mg/kg oral rat
Oxybuprocaine HCl	N/A
Oxymetazoline HCl	LD_{50} 0.88 mg/kg oral rat
Oxytetracycline	LD_{50} 4700 mcg/kg oral mouse; LD_{50} 680 mcg/kg oral rat
Paracetamol	LD_{50} 2404 mg/kg oral rat
Papaverine hydrochloride	LD_{50} 68.8 mg/kg oral rat
Paroxetine HCl hemihydrate	LD_{50} 374 mg/kg oral rat; LD_{50} 341 mg/kg oral mouse
Penicillamine	LD_{50} 3670 mg/kg oral mouse
Pentoxifylline	LD_{50} 1170 mg/kg oral rat

Your Company's Logo **Your Company's Name**

Active Ingredients	Toxicity
Phenobarbital sodium	LD_{50} 150 mg/kg oral rat
Phenylephrine HCl	LD_{50} 350 mg/kg oral rat
Phenylalanine	Not known
Piperazine citrate	LD_{50} 11,200 mg/kg oral rat
Propranolol HCl	LD_{50} 466 mg/kg oral rat
Prazosin hydrochloride	LD_{50} 1950 mg/kg oral rat
Prednisolone	LD_{50} 1680 mg/kg oral mouse
Promethazine HCl	LD_{50} 255 mg/kg oral rat
Procaine hydrochloride	LD_{50} 184 mg/kg IP rat; LD_{50} 180 mg/kg IP mouse
Pheniramine maleate	LD_{50} 520 mg/kg oral rat
Pseudoephedrine HCl	LD_{50} 202 mg/kg IP mouse
Ranitidine HCl	LD_{50} >5 mg/kg oral rat; LD_{50} 884 mg/kg
Recombinant human erythropoietin	N/A
Resorcinol	LD_{50} 301 mg/kg oral rat
Rifampicin	Not known
Risperidone	LD_{50} 56.6 mg/kg oral rat
Salbutamol sulfate	LD_{50} 1950 mg/kg oral mouse; LD_{50} 2500 mg/kg oral rat
Salicylamide	LD_{50} 1700 mg/kg oral rat
Salicylic acid	LD_{50} 1500 mg/kg oral mouse; LD_{50} 700 mg/kg oral rat
Sertaconazole nitrate	Not available
Silver sulfadiazine	LD_{50} 1000 mg/kg oral rat
Simvastatine sodium	LD_{50} 4438 mg/kg oral rat; LD_{50} 3.0 g/kg oral mouse
Sodium alendronate	Not available
Sodium citrate	Not known
Sodium valproate	LD_{50} 870 mg/kg oral rat
Sodium iodide	LD_{50} 4340 mg/kg oral rat
Somatostatin	LD_{50} 21 mg/kg IV rat; LD_{50} 33 mg/kg IV mouse
Simethicone	LD_{50} 2000 mg/kg oral rat
Sucralfate	LD_{50} 12 g/kg oral rat
Succinylsulfathiazole	LD_{50} 10 g/kg IV rat; LD_{50} 5700 mg/kg IP mouse
Tamoxifene citrate	LD_{50} 1190 g/kg oral rat
Tetracycline HCl	LD_{50} 6443 mg/kg oral rat; LD_{50} 2759 mg/kg oral mouse
Theophylline	LD_{50} 666 mg/kg oral rat
Tribenoside	LD_{50} 10.0 mg/kg oral rat
Triamcinolone acetonide	LD_{50} 5000 mg/kg oral mouse
Triprolidine HCl	LD_{50} 840 mg/kg oral rat; LD_{50} 495 mg/kg oral mouse
Trimethoprim	LD_{50} >5300 mg/kg oral rat; LD_{50} 2764 mg/kg oral mouse
Tyrothricin	LD_{50} >3000 mg/kg oral mouse
Xylometazoline	LD_{50} 230.0 mg/kg oral rat
Vancomycin HCl	LD_{50} 10.0 g/kg oral rat; LD_{50} 5.0 g/kg oral mouse

continued

Your Company's Logo **Your Company's Name**

Active Ingredients	Toxicity
Verapamil hydrochloride	LD_{50} 108.0 mg/kg oral rat
Vitamin A	LD_{50} 7910 mg/kg oral rat; LD_{50} 6060 mg/kg oral mouse
Vitamin D	LD_{50} 2000 mg/kg oral rat
Vitamin C	LD_{50} 11,900 mg/kg oral rat
Vitamin B_1	LD_{50} 10,000 mg/kg oral rat and oral mouse
Vitamin B_2	LD_{50} 20,000 mg/kg oral rat
Vitamin B_6	LD_{50} 5500 mg/kg oral mouse; 4000 mg/kg oral rat
Vitamin B_{12}	LD_{50} 8000 mg/kg oral mouse
Xylometazoline hydrochloride	LD_{50} 230 mg/kg oral rat; LD_{50} 75 mg/kg oral mouse
Zinc oxide	LD_{50} >8437.0 mg/kg oral rat; LD_{50} 7950 mg/kg oral mouse

CLV-17

Cleaning Validation Products Grouping Matrix (Tablets, Capsules, and PPS)

Your Company's Logo **Your Company's Name**

In the following sections, a general presentation of product grouping along with the information about their APIs, excipients, therapeutic dose, maximum daily dosage, solubility, and toxicity is presented. The basic purpose of products grouping is to determine the representative or worst-case products manufactured in a particular equipment train.

While generating the CVMP, it is very important to have a clear overview of all the product types and knowledge of their constituents. Based on this information and with the help of equipment trains in the following sections, it would be a straightforward process to identify the worst-case products for each equipment train.

The information is general and is only meant to explain how the step-by-step generation of Master Validation Plan (MVP) should be processed.

17.1 Product Grouping Matrix (Solid Dosage)

17.1.1 Tablets

Product	Batch Size	Ingredients	Therapeutic Dose	Maximum Usage per Day	Solubility	Toxicity Level LD_{50}
Thidoxine tablets	450,000	Thiamine	100 mg	440 mg	2	LD_{50} >10,000 mg/kg oral rat
		Pyridoxine	200 mg	840 mg	2	LD_{50} 5500 mg/kg oral mouse
		Lactose monohydrates			2	
		PVP-90			1	
		Magnesium stearate			7	
		Avicel PH-112			7	
		Cyanocobalamine	200 mg	1.208 mg	4	LD_{50} 2 g/kg oral mouse
Aceclofenac F/C tablets	600,000 (120 kg)	Aceclofenac	100 mg	200 mg	7	
		Lactose			2	
		Maize starch			3	

continued

Your Company's Logo

Your Company's Name

Product	Batch Size	Ingredients	Therapeutic Dose	Maximum Usage per Day	Solubility	Toxicity Level LD_{50}
		PVP-K-30			2	
		Avicel			7	
		Magnesium stearate			7	
Paracetamol 500 mg tablets	1,000,000 tablets (640 kg)	Paracetamol	500 mg	4 g	3	LD_{50} 2404 mg/kg oral rat
		Maize starch			3	
		PVP-K-30			2	
		Potassium sorbate			1	
		Glycerol			5	
Albendazole tablets	175,000 (103.25 kg)	Albendazole	400 mg	800 mg	7	LD_{50} 2400 mg/kg oral rat
		Maize starch			3	
		Lactose			2	
		PVP-K-30			2	
		Magnesium stearate			7	
		Avicel			7	
		Primogel			6	
Amiodarone 200 mg tablets	500,000 (175 kg)	Amiodarone HCl	200 mg	600 mg	6	LD_{50} 2600 mg/kg oral rat
		Lactose			2	
		PVP-K-30			2	
		Magnesium stearate			7	
		Aerosil 200			7	
		Maize starch			3	
Bromocryptin 2.5 mg tablets	1,000,000 (110 kg)	Bromocryptin	2.5 mg	7.5 mg	7	
		Lactose monohydrates			2	
		Maize starch			3	
		Sodium EDTA			3	
		Magnesium stearate			7	
		Aerosil 200			7	
Ketotifen 1.0 mg tablets	500,000 tablets (57.5 kg)	Ketotifen fumarate	1 mg	2 mg	5	LD_{50} 360 mg/kg oral rat
		Lactose monohydrates			2	
		Maize starch			3	

Your Company's Logo **Your Company's Name**

Product	Batch Size	Ingredients	Therapeutic Dose	Maximum Usage per Day	Solubility	Toxicity Level LD_{50}
		PVP-K-30			2	
		Magnesium stearate			7	
		Avicel PH-102			7	
Oxybuprocaine Lozenges	100,000 (124.5 kg)	Oxybuprocaine HCl	0.2 mg	1.2 mg	1	
		Cetyl pyridinium	1.0 mg	6.0 mg	1	
		Tyrothricin	4.0 mg	24 mg		
		Menthol			7	
		Aerosil 200			7	
		Magnesium stearate			7	
		Sorbitol			4	
		Dextrose				
Betamethasone 0.5 mg tablets	1,000,000 tablets (110 kg)	Betamethasone	0.5 mg	5 mg	7	LD_{50} 3.0 g/kg oral rat
		Magnesium stearate			7	
		Lactose monohydrates			2	
		Maize starch			3	
Salbutamol 4 mg tablets	1,000,000 tablets (120 kg)	Salbutamol	4 mg	16 mg	2	LD_{50} 1950 mg/kg oral mouse; LD_{50} 2500 mg/kg oral rat
		Lactose monohydrates			2	
		Maize starch			3	
		Magnesium stearate			7	
Captopril 50 mg tablets	500,000 tablets	Captopril			2	LD_{50} 4245 mg/kg oral rat
		Lactose spray dried			2	
		Avicel PH-102			7	
		Stearic acid			7	
		Starch 1500			5	
Propranolol 40 mg tablets	1,000,000 tablets (200 kg)	Propranolol HCl	40 mg	120 mg	3	Not known
		Maize starch			3	
		Lactose			2	
		Magnesium stearate			7	

continued

Your Company's Logo

Your Company's Name

Product	Batch Size	Ingredients	Therapeutic Dose	Maximum Usage per Day	Solubility	Toxicity Level LD_{50}
		Stearic acid			7	
		Avicel			7	
Cetrizine 10 mg F/C tablets	800,000 tablets (104 kg)	Cetrizine HCl	10 mg	10 mg	2	LD_{50} 703 mg/kg oral rat
		Maize starch			3	
		Lactose			2	
		PVP-K-30			2	
		Magnesium stearate			7	
Chlorpheniramine tablets	2,000,000 tablets	Chlorpheniramine maleate	4 mg	24 mg/ day	2	LD_{50} 130 mg/kg oral mouse; LD_{50} 300 mg/kg oral rat
		Lactose monohydrates			2	
		Maize starch			3	
		Magnesium stearate			7	
Cimetidin 400 mg tablets	225,000 tablets (123.75 kg)	Cimetidin	800 mg	1600 mg	5	LD_{50} 5000 mg/kg oral rat
Ciprofloxacin 500 mg F/C tablets	150,000 tablets (115.5 kg)	Ciprofloxacin HCl	500 mg	500 mg	4	LD_{50} 5000 mg/kg oral rat; LD_{50} 5000 mg/kg oral mouse
		Kolidone CL			7	
		Primogel			6	
		PVP-K-30			2	
		Magnesium stearate			7	
		Avicel PH-102			7	
		Aerosil 200			7	
Clarithromycin 500 mg tablets	125,000 tablets (112 kg)	Clarithromycin	500 mg	1500 mg	7	
		Avicel PH-102			7	
		PVP-K-30			2	
		Aerosil 200			7	
		Starch 1500			5	
		Stearic acid			7	
Diclofenac 50 mg tablets	2,000,000 tablets (438 kg)	Diclofenac sodium	50 mg	150 mg	4	LD_{50} 150 mg/kg oral rat
		Lactose monohydrates			2	

Your Company's Logo **Your Company's Name**

Product	Batch Size	Ingredients	Therapeutic Dose	Maximum Usage per Day	Solubility	Toxicity Level LD_{50}
		Maize starch			3	
		Magnesium stearate			7	
		Avicel			7	
		PVP-K-30			2	
		Aerosil 200			7	
Metformin 100 mg F/C tablets	100,000 tablets (11.5 kg)	Metformin HCl	1000 mg	1000 mg	2	LD_{50} 4000 mg/kg oral rat
		Starch 1500			5	
		Maize starch			3	
		PVP-K-30			2	
		PVP-K-90			2	
		Avicel PH-101			7	
		Magnesium stearate			7	
Diazepam 5 mg tablets	1,000,000 tablets (120 kg)	Diazepam	5 mg	60 mg	6	LD_{50} 48 mg/kg oral mouse
		Lactose monohydrates			2	
		Maize starch			3	
		Magnesium stearate			7	
		PVP-K-30			2	
Dimenhydrinate tablets	1,000,000 tablets (211 kg)	Dimenhydrinate	50 mg	400 mg	5	LD_{50} 681 mg/kg oral rat
		Lactose monohydrates			2	
		Maize starch			3	
		Magnesium stearate			7	
Erythromycin 500 mg tablets	115,000 tablets (120.75 kg)	Erythromycin stearate	500 mg	1000 mg	7	LD_{50} >10.0 g/kg oral mouse
		Maize starch			3	
		PVP-K-30			2	
		Primogel			6	
		Stearic acid			7	
		Magnesium hydroxide			7	
		Glyceryl behenate			7	

continued

Your Company's Logo **Your Company's Name**

Product	Batch Size	Ingredients	Therapeutic Dose	Maximum Usage per Day	Solubility	Toxicity Level LD_{50}
Dextromethorphan tablets	700,000 tablets (84 kg)	Dextromethorphan HBr			2	LD_{50} 350 mg/kg oral rat
		Maize starch			3	
		Lactose monohydrates			2	
		Magnesium stearate			7	
Famotidine 40 mg tablets	600,000 tablets (123 kg)	Famotidine	40 mg	80 mg/ tablet	6	LD_{50} 4049 mg/kg oral rat
		Avicel			7	
		Starch 1500			5	
		PVP-K-25			2	
		Glyceryl behenate			7	
		Iron oxide				
Carbamazepine tablets 200 mg	250,000 tablets (65 kg)	Carbamazepine	200 mg	200 mg	5	LD_{50} 1957 mg/kg oral rat
		Avicel PH-101			7	
		Aerosil 200			7	
		Magnesium stearate			7	
		CMC sodium			3	
		Primogel			6	
Antiflu tablets	1,000,000 tablets (620 kg)	Paracetamol	200 mg	4000 mg	3	LD_{50} 2404 mg/kg oral rat
		Salicylamide	250 mg	4.5 mg		LD_{50} 1700 mg/kg oral rat
		Phenylephrine	5 mg			LD_{50} 350 mg/kg oral rat
		Promethazine HCl	5 mg			LD_{50} 255 mg/kg oral rat
		Maize starch			3	
		PVP-K-30			2	
		Magnesium stearate			7	
		Aerosil 200			7	
Folic acid 5 mg tablets	6,000,000 tablets (690 kg)	Folic acid	5 mg	5 mg/ day	7	LD_{50} >8000 mg/ kg oral rat
		Lactose monohydrates			2	
		Maize starch			3	

Your Company's Logo **Your Company's Name**

Product	Batch Size	Ingredients	Therapeutic Dose	Maximum Usage per Day	Solubility	Toxicity Level LD_{50}
		Avicel PH-102			7	
		Stearic acid			7	
		Aerosil 200			7	
Gliclazide 80 mg tablets	500,000 tablets (80 kg)	Gliclazide coarse	80 mg	160 mg	7	LD_{50} 3000 mg/ kg oral rat
		Lactose monohydrates			2	
		Maize starch			3	
		PVP-K-30			2	
		Magnesium stearate			7	
		Avicel PH-102			7	
		Primogel			6	
Prednisolone 20 mg tablets	750,000 tablets (187.5 kg)	Prednisolone Magnesium stearate	20 mg	200 mg	6 7	LD_{50} 1680 mg/kg oral mouse
		Lactose			2	
		Avicel			7	
Promethasone 25 mg F/C	600,000 tablets (20 kg)	Promethasone	25 mg	50 mg	1	LD_{50} 255 mg/kg oral rat
		Lactose monohydrates			2	
		Maize starch			3	
		PVP-K-30			2	
		Magnesium stearate			7	
		Sodium disulfate				
Indapamide 2.5 mg F/C tablets	1,000,000 tablets (95 kg)	Indapamide	2.5 mg	2.5 mg	7	LD_{50} >3000 mg/kg oral rat
		Lactose monohydrates			2	
		PVP-K-30			2	
		Maize starch			3	
		Magnesium stearate			7	
		Sodium lauryl sulfate				
Diphenoxylate	1,000, 000 tablets	Diphenoxylate HCl	2.5 mg	30 mg	4	LD_{50} 600 mg/kg oral rat
Atropine tabs		Atropine sulfate	0.025 mg	0.3 mg		
		Lactose monohydrates			2	

continued

Your Company's Logo

Your Company's Name

Product	Batch Size	Ingredients	Therapeutic Dose	Maximum Usage per Day	Solubility	Toxicity Level LD_{50}
		Maize starch			3	
		Magnesium stearate			7	
Levofloxacin F/C tablets	160,000 tablets (105.6 kg)	Levofloxacin	500 mg	1000 mg		LD_{50} 35,900 mg/kg oral rat; LD_{50} 3366 mg/kg oral mouse
		Avicel PH-102			7	
		PVP-K-30			2	
		Hypromellose				
Paracetamol caplet 500	1,000,000 tablets (640 kg)	Paracetamol	500 mg	2000 mg	3	LD_{50} 2404 mg/kg oral rat
		Maize starch			3	
		PVP-K-30			2	
		Magnesium stearate			7	
		Gelatin			7	
		Glycerol			5	
		Primogel			6	
		Aerosil 200			7	
Aspirin 81 mg E/C tablets	2,000,000 tablets (230 kg)	Aspirin	81 mg	4 g/day	5	LD_{50} 200 mg/kg oral rat
		Avicel PH-102			7	
		Magnesium stearate			7	
Aspirin 300 mg E/C tablets	2,000,000 tablets	Aspirin	300 mg		5	LD_{50} 200 mg/kg oral rat
		Avicel PH-102			7	
		Magnesium stearate			7	
Attapulgite tablets	120,000 tablets (120 kg)	Attapulgite regular	19 kg	750 mg	1500 mg	Nontoxic
		Attapulgite colloidal	11 kg		880 mg	
		Klucel				
		Sucrose				
		Magnesium stearate				
		PVP-K-30				
Lamotrigine 100 mg tablets	150,000 tablets (45 kg)	Lamotrigine	100 mg	200 mg	6	LD_{50} 185 mg/kg oral rat; LD_{50} 269 mg/kg oral mouse

Your Company's Logo **Your Company's Name**

Product	Batch Size	Ingredients	Therapeutic Dose	Maximum Usage per Day	Solubility	Toxicity Level LD_{50}
		Avicel PH-102			7	
		Lactose monohydrates			2	
		Primogel			6	
		PVP-K-30			2	
		Iron oxide yellow			7	
Sennosides 12 mg S/C tablets	1,300,000 tablets (178.75 kg)	Sennosides	12 mg	72 mg/ day	2	
		Avicel PH-102			7	
		Magnesium stearate			7	
		Lactose dried			2	
		Starch 1500				
		Aerosil 200			7	
Bisacodyl 5 mg tablets	650,000 tablets (48.75 kg)	Bisacodyl	5 mg	20 mg	6	LD_{50} 4320 mg/kg oral rat
		Lactose			2	
		Avicel			7	
		Maize starch			3	
		Magnesium stearate			7	
Benzafibrate 200 mg tablets	3,000,000 tablets (111 kg)	Benzafibrate	200 mg	600 mg	7	LD_{50} 1082.0 mg/kg oral rat
		Maize starch			3	
		Magnesium stearate			7	
		Methocel			3	
		Avicel			7	
		Primogel			6	
		Lactose monohydrates			2	
Lomefloxacin 400 mg tablets	150,000 tablets (102.6 kg)	Lomefloxacin HCl	400 mg	400 mg	5	LD_{50} 1556 mg/kg oral rat
		Lactose monohydrates			2	
		CMC calcium			3	
		Klucel EF			3	
		Magnesium stearate			7	
		Avicel PH-102			7	

continued

Your Company's Logo

Your Company's Name

Product	Batch Size	Ingredients	Therapeutic Dose	Maximum Usage per Day	Solubility	Toxicity Level LD_{50}
Acyclovir 800 mg tablets	90,000 tablets (97.65 kg)	Acyclovir	800 mg	2400 mg	3	LD_{50} >20.0 g/kg oral rat
		Avicel PH-102			7	
		Primogel			6	
		Maize starch			3	
		Magnesium stearate			7	
Loratadine 10 mg tablets	1,000,000 tablets (115 kg)	Loratadine	10 mg	10 mg	7	Nontoxic
		Lactose monohydrates			2	
		Maize starch			3	
		Magnesium stearate			7	
Mebendazole 100 mg tablets	150,000 tablets (43. 05 kg)	Mebendazole	100 mg	100 mg	7	LD_{50} 714 mg/kg oral rat
		Maize starch			3	
		Avicel PH-102			7	
		PVP-K-30			2	
Methyldopa 250 mg F/C tablets	285,000 tablets (101.175)	Methyldopa anhydrous			4	
		Guar gum			7	
		Avicel PH-102				
		Aerosil 200			7	
		Ethyl cellulose				
		Magnesium stearate			7	
Glibenclamide tablets	500,000 tablets (80 kg)	Glibenclamide	2.5 mg	20 mg/ day	6	LD_{50} >20,000 mg/kg oral rat
		Lactose monohydrates			2	
		Maize starch			3	
		Magnesium stearate			7	
		Aerosil 200			7	
		Talc fine powder			7	
Multivitamin M tablets	1,300,000 tablets (240 kg)	Thiamine	2 mg	6 mg/ day	2	LD_{50} >1000 mg/kg oral rat
		Riboflavin	1 mg	3 mg/ day	2	LD_{50} >20,000 mg/kg oral rat

Your Company's Logo **Your Company's Name**

Product	Batch Size	Ingredients	Therapeutic Dose	Maximum Usage per Day	Solubility	Toxicity Level LD_{50}
		Nicotinamide	15 mg	45 mg/day	2	LD_{50} 3500 mg/kg oral rat
		Vitamin D_3	300 IU	900 IU/day	7	LD_{50} >2000 mg/kg oral rat
		Vitamin A palmitate	3000 IU	9000 IU/day	7	LD_{50} 7910 mg/kg oral rat
		PVP-K-30			2	
		Avicel PH-102			7	
		Magnesium stearate			7	
		Lactose monohydrates			2	
		Magnesium oxide			7	
		Zinc sulfate			7	
Bromhexine 8 mg tablets	2,000,000 tablets (240 kg)	Bromhexine HCl	8 mg	48 mg	6	LD_{50} 1226 mg/kg oral mouse
		Lactose monohydrates			2	
		Maize starch			3	
		Gelatin powder			7	
		Magnesium stearate			7	
Ambroxol 30 mg tablets	350,000 tablets (84 kg)	Ambroxol HCl	30 mg	60 mg	4	LD_{50} 13,400.0 mg/kg oral rat
		Lactose monohydrates			2	
		Maize starch			3	
		Aerosil 200/AC-DI-So1			7–7	
		Magnesium stearate			7	
Orphenadrine tablets	1,000,000 tablets (660 kg)	Paracetamol	450 mg	3600 mg	3	LD_{50} 2404 mg/kg oral rat
		Orphenadrine citrate	35 mg		4	LD_{50} 150 mg/kg oral mouse
		Maize starch			3	
		PVP-K-30			2	
		Primogel			6	
		Glycerol			5	
Enalapril 20 mg tablets	200,000 tablets (40 kg)	Enalapril maleate	20 mg	20 mg	3	LD_{50} 2973 mg/kg oral rat
		Lactose monohydrates			2	

continued

Your Company's Logo

Your Company's Name

Product	Batch Size	Ingredients	Therapeutic Dose	Maximum Usage per Day	Solubility	Toxicity Level LD_{50}
		Magnesium stearate			7	
		Maize starch			3	
		Starch 1500			5	
Metronidazole 500 mg tablets	625,000 tablets (593.75 kg)	Metronidazole	500 mg	2000 mg	4	LD_{50} 3000 mg/kg oral rat
		Lactose monohydrates			2	
		Avicel PH-102			7	
		Maize starch			3	
		PVP-K-30			2	
		Magnesium stearate			7	
		Primogel			6	
Mebendazole 100 mg tablets	400,000 tablets (116 kg)	Mebendazole	100 mg	200 mg	7	LD_{50} 714 mg/kg oral rat; LD_{50} 620mg/kg oral mouse
		Avicel PH-102			7	
		PVP-K-30			2	
		Primogel			6	
		Magnesium stearate			7	
		Sodium saccharin			2	
		Sodium lauryl sulfate			2	
Ibuprofen 600 mg tablets	650,000 tablets (562.25 kg)	Ibuprofen	600 mg	2400 mg	7	LD_{50} 636 mg/kg oral rat
		Maize starch			3	
		Magnesium stearate			7	
		Starch 1500			5	
		Aerosil 200			7	
		Stearic acid			7	
Metoclopramide 10 mg tablets	1,000,000 tablets (125 kg)	Metoclopramide	10 mg	30 mg/ day	1	LD_{50} 280 mg/kg oral mouse
		Lactose monohydrates			2	
		Maize starch			3	
		Microcrystalline cellulose			3	

Your Company's Logo **Your Company's Name**

Product	Batch Size	Ingredients	Therapeutic Dose	Maximum Usage per Day	Solubility	Toxicity Level LD_{50}
Pyridoxine 40 mg tablets	2,000,000 tablets (240 kg)	Pyridoxine HCl	40 mg	1200 mg	2	LD_{50} 5500 mg/kg oral mouse
		Microcrystalline cellulose			3	
		Magnesium stearate			7	
		Aerosil 200			7	
Ranitidine 300 mg F/C tablets	250,000 tablets (120 kg)	Ranitidine HCl	300 mg	600 mg	1	LD_{50} >5 mg/kg oral rat; LD_{50} 884 mg/kg
		Magnesium stearate			7	
		Avicel PH-102			7	
Clarithromycin 500 tablets	125,000 tablets (112.5 kg)	Clarithromycin	500 mg	1500 mg	7	
		Avicel PH-102			7	
		PVP-K-30			2	
		Aerosil 200			7	
		AC-DI-So1			7	
		Magnesium stearate			7	
		Stearic acid			7	
Simethicone tablets	400,000 tablets (252 kg)	Simethicone	42 mg	336 mg	7	LD_{50} >2000 mg/kg oral rat
		Magnesium stearate			7	
		Dextrates			2	
Furosemide 40 mg tablets	500,000 tablets (100 kg)	Furosemide	40 mg	40 mg	4	LD_{50} 2600 mg/kg oral rat
		Maize starch			3	
		Lactose monohydrates			2	
		Starch 1500			5	
		Stearic acid			7	
		Aerosil 200			7	
		Magnesium stearate			7	
Ciprofloxacin 500 F/C tablets	150,000 tablets (115.5 kg)	Ciprofloxacin HCl	500 mg	1500 mg	7	LD_{50} >500 mg/kg oral rat
		Kolidone			7	
		Primogel			6	

continued

Your Company's Logo

Your Company's Name

Product	Batch Size	Ingredients	Therapeutic Dose	Maximum Usage per Day	Solubility	Toxicity Level LD_{50}
		PVP-K-30			2	
		Aerosil 200			7	
		Magnesium stearate			7	
		Avicel PH-102			7	
Hyoscine butyl S/C tablets	2,600,000 tablets (202.8 kg)	Hyoscine butyl	10 mg	100 mg	2	LD_{50} 1040 mg/kg oral rat
		Lactose monohydrates			2	
		Magnesium stearate			7	
		Maize starch			3	
		Starch 1500				
		PVP-K-30			2	
Pseudoephedrine tablets	500,000 tablets	Triprolidine HCl	2.5 mg	7.5 mg	3	LD_{50} 840 mg/kg oral rat
		Pseudoephedrine HCl	60 mg	180 mg	2	LD_{50} 202 mg/kg IP mouse
		Lactose monohydrates			2	
		Maize starch			3	
		PVP-K-30			2	
		Magnesium stearate			7	
Simvastatin 20 mg tablets	500,000 tablets (100 kg)	Simvastatin sodium	20 mg	40 mg	7	LD_{50} 4438 mg/kg oral rat; LD_{50} 3.0 g/kg oral mouse
		Lactose monohydrates			2	
		Starch 1500			5	
		Avicel PH-102			7	
		Ascorbic acid				
		Aerosil 200			7	
		Magnesium stearate			7	
Tamoxifen 10 mg tablets	500,000 tablets (87.5 kg)	Tamoxifen citrate	10 mg	20 mg	5	LD_{50} 1190 g/kg oral rat
		Lactose monohydrates			2	
		Maize starch			3	
		Magnesium stearate			7	

Your Company's Logo **Your Company's Name**

Product	Batch Size	Ingredients	Therapeutic Dose	Maximum Usage per Day	Solubility	Toxicity Level LD_{50}
		PVP-K-30			2	
		AC-DI-So1			7	
Atenolol 100 mg F/C tablets	250,000 tablets (100 kg)	Atenolol	50 mg	100 mg	4	LD_{50} 2000.0 mg/kg oral mouse/rat
		Maize starch			3	
		Magnesium carbonate			7	
		Sodium lauryl sulfate			2	
		Avicel PH-102			7	
		Magnesium stearate			7	
		Primogel			6	
Thiamine 100 mg tablets	375,000 tablets (78.75 kg)	Thiamine HCl	100 mg	100 mg	4	LD_{50} >10,000 mg/kg oral rat
		Lactose monohydrates			2	
		Kollidone CL			7	
		PVP-K-90			2	
		Magnesium stearate			7	
		Avicel PH-112			7	
Trimethoprim DS tablets	750,000 tablets (825 kg)	Sulfamethoxazole	400 mg	3 g/day	2	
		Trimethoprim	80 mg		6	LD_{50} >5300 mg/kg oral rat; LD_{50} 2764 mg/kg oral mouse
		Maize starch			3	
		Magnesium stearate			7	
		Gelatin			7	
		Guar gum				
		Sodium lauryl sulfate			2	
Norfloxacin 400 mg F/C tablets	200,000 tablets (104 kg)	Norfloxacin	400 mg	800 mg	5	LD_{50} >4000 mg/kg oral rat
		Avicel PH-102			7	
		AC-DI-So1			7	
		Magnesium stearate			7	
Valproate 500 mg E/C tablets	200,000 tablets (200 kg)	Sodium valproate				LD_{50} 870 mg/kg oral rat

continued

Your Company's Logo

Your Company's Name

Product	Batch Size	Ingredients	Therapeutic Dose	Maximum Usage per Day	Solubility	Toxicity Level LD_{50}
		Magnesium stearate			7	
		Avicel PH-112			7	
		Maize starch			3	
		AC-DI-So1			7	
		Aerosil 200			7	
B-complex tablets	7,500,000 tablets (682.8 kg)	Calcium pantothenate	3 mg	150 mg	2	LD_{50} 10 g/kg oral rat
		Pyridoxine	2 mg	60 mg	2	LD_{50} 5500 mg/kg oral mouse
		Riboflavin base	2 mg	60 mg	2	LD_{50} >40,000 mg/kg oral mouse
		Magnesium stearate			7	
		Aerosil 200			7	
		Thiamine mononitrate	2 mg	120 mg	2	LD_{50} >10,000 mg/kg oral rat
Vitamin C 500 mg tablets	300,000 tablets (390 kg)	Ascorbic acid	170 mg	340 mg	2	LD_{50} 1190 mg/kg oral rat
		Sodium ascorbate		776 mg	2	
		Magnesium stearate			7	
		Sorbitol			4	
		Dextrates			2	

17.2 Product Grouping Matrix (Capsules)

Product	Batch Size	Ingredients	Therapeutic Dose (mg)	Maximum Usage per Day	Solubility	Toxicity Level LD_{50}
Indomethacin 25 mg tablets	500,000 capsules (125 kg)	Indomethacin	25	200 mg	1	LD_{50} 2.42 mg/kg oral rat
		AC-DI-So1			7	
		Lactose monohydrates			2	
		Magnesium stearate			7	
		Aerosil 200			7	
		Sodium lauryl sulfate			2	

Your Company's Logo **Your Company's Name**

Product	Batch Size	Ingredients	Therapeutic Dose (mg)	Maximum Usage per Day	Solubility	Toxicity Level LD_{50}
Tetracycline HCl 250 mg	750,000 capsules (243.75 kg)	Tetracycline HCl	250	4 g	3	LD_{50} 6443 mg/kg oral rat
		Lactose monohydrates			2	
		Aerosil 200			7	
		Magnesium stearate			7	
Oxytetracycline HCl 250 mg	750,000 capsules (234 kg)	Oxytetracycline HCl	250	2 g/day	2	LD_{50} 4700 mg/kg oral rat
		Maize starch			3	
		Aerosil 200			7	
		Talc fine			7	
		Magnesium stearate			7	
Doxycycline 100 mg	150,000 capsules (23.25 kg)	Doxycycline hyclate	100	200 mg	3	LD_{50} 1900.0 g/kg oral mouse
		Avicel PH-102			7	
		Maize starch			3	
		Sodium lauryl sulfate			2	
		Magnesium stearate			7	
		Aerosil 200			7	
Carbinoxamine	50,000 capsules	Carbinoxamine maleate	10	10 mg	2	LD_{50} 162 mg/kg oral mouse
		Phynyle propano-lamine HCl				
Fluoxetine 20 mg capsule	500,000 capsules (77.5 kg)	Fluoxetine HCl	20	20 mg	5	LD_{50} 452 mg/kg oral rat
		Maize starch			3	
		Aerosil 200			7	
		Simethicone			7	
Azithromycin 250 mg	100,000 capsules (52 kg)	Azithromycin	250	500 mg	5	LD_{50} >3.0 g/kg oral rat
		Maize starch			3	
		Sodium lauryl sulfate			2	
		Anhydrous lactose			2	

Your Company's Logo

Your Company's Name

17.3 Product Grouping Matrix (Granules)

Product	Batch Size	Ingredients	Therapeutic Dose (mg)	Maximum Usage per Day	Solubility	Toxicity Level LD_{50}
Azithromycin 200 mg powder to prepare suspension (PPS)	4000 bottles	Azithromycin dihydrate	200 mg	600 mg	5	LD_{50} >3.0 g/kg oral rat
		Caster sugar			3	
		Sodium phosphate tribasic			2	
		Sodium benzoate			2	
		Klucel			3	
Erythromycin 200 mg/5 mL	935 kg	Erythromycin Ethyl succinate	200 mg	1000 mg	7	LD_{50} >10.0 g/kg oral rat
		Sodium CMC			3	
		FD&C Red # 40			3	
		Sucrose			1	
		Sodium saccharin			2	
		Sodium citrate			2	
		Xanthan gum			3	
		Simethicone			7	

In the preceding chapters, we have presented matrices for equipment details, solubility, and toxicity of active materials as well as products grouping with the concentration and daily maximum dosage of the actives in the table above. After having all these information, it is important for the validation professional to build the equipment train for the different dosage forms.

All the products are processed through an equipment train. For example, a tablet product is processed through a granulator, a mill, a blender, and a tablet press. The amount of contamination that may be present in the finished product is contributed from each individual piece of equipment in this train. Together with the help of information obtained in the previous chapters and equipment trains allocated, shown in the next chapter, selection of worst case for cleaning validation will be carried out for each and every category of products. The worst case related to product is the one containing most insoluble active ingredient, with lowest lethal dose or with highest therapeutic dose.

CLV-18

Product/Equipment Train Matrix (Tab–Cap–PPS)

Your Company's Logo

Your Company's Name

18.1 Products/Equipment Train (Tablets, Capsules, and PPS)

18.1.1 Wet Granulation Uncoated Tablets

Product	Equipments
Paracetamol 500 mg tablets	Granulator, fluid bed dryer, sifter, tumbler, tablet press A
Salbutamol 4 mg tablets	Granulator, fluid bed dryer, sifter, tumbler, tablet press B
Ketotifen tablets	Granulator, fluid bed dryer, sifter, tumbler, tablet press B
Sulfamethoxazole DS tablets	Granulator, fluid bed dryer, sifter, tumbler, tablet press B
Mini glibenclamide tablets	Granulator, fluid bed dryer, sifter, tumbler, tablet press A
Pseudoephedrine tablets	Granulator, fluid bed dryer, sifter, tumbler, tablet press B
Glibenclamide tablets	Granulator, fluid bed dryer, sifter, tumbler, tablet press A
Gliclazide 80 mg tablets	Granulator, fluid bed dryer, sifter, tumbler, tablet press B
Dimenhydrinate tablets	Granulator, fluid bed dryer, sifter, tumbler, tablet press B
Antiflu tablets	Granulator, fluid bed dryer, sifter, tumbler, tablet press A
Chlorohistol maleate tablets	Granulator, fluid bed dryer, sifter, tumbler, tablet press A/B
Diazepam 5 mg tablets	Granulator, fluid bed dryer, sifter, tumbler, tablet press A/B
Al–Mg hydroxide tablets	Granulator, fluid bed dryer, sifter, tumbler, tablet press A/B
Betamethasone 0.5 mg tablets	Granulator, fluid bed dryer, sifter, tumbler, tablet press B
Carbamazepine tablets	Granulator, fluid bed dryer, sifter, tumbler, tablet press B
Gliclazide tablets	Granulator, fluid bed dryer, sifter, tumbler, tablet press B
Indapamide tablets	Granulator, fluid bed dryer, sifter, tumbler, tablet press B
Loratadine tablets	Granulator, fluid bed dryer, sifter, tumbler, tablet press B
Enalapril tablets	Granulator, fluid bed dryer, sifter, tumbler, tablet press B/C
Furosemide tablets	Granulator, fluid bed dryer, sifter, tumbler, tablet press B/C
Al–Mg hydroxide plus tablets	Granulator, fluid bed dryer, sifter, tumbler, tablet press A/B
Orphenadrine/acetamol tablets	Granulator, fluid bed dryer, sifter, tumbler, tablet press B
Amiodarone tablets	Granulator, fluid bed dryer, sifter, tumbler, tablet press C
Diphenhydramine II tablets	Granulator, fluid bed dryer, sifter, tumbler, tablet press C
Bromocryptin tablets	Granulator, fluid bed dryer, sifter, tumbler, tablet press C
Diphenoxylate tablets	Granulator, fluid bed dryer, sifter, tumbler, tablet press B
Paracetamol (dol) tablets	Granulator, fluid bed dryer, sifter, tumbler, tablet press A
Ambroxol 30 mg tablets	Granulator, fluid bed dryer, sifter, tumbler, tablet press C

continued

Your Company's Logo **Your Company's Name**

Product	Equipments
Tamoxifen tablets	Granulator, fluid bed dryer, sifter, tumbler, tablet press B
Thiamine 100 tablets	Granulator, fluid bed dryer, sifter, tumbler, tablet press B
Norfloxacin tablets	Granulator, fluid bed dryer, sifter, tumbler, tablet press B

18.1.2 Wet Granulation Coated Tablets

Product	Equipments
Bezafibrate 200 mg tablets	Granulator, fluid bed dryer, sifter, tumbler, tablet press B, cota
Ibuprofen 600 mg tablets	Granulator, fluid bed dryer, sifter, tumbler, tablet press B, cota
Cimetidine 200/400/800 mg	Granulator, fluid bed dryer, sifter, tumbler, tablet press B, cota
Erythromycin 500 mg tablets	Granulator, fluid bed dryer, sifter, tumbler, tablet press B, cota
Ciprofloxacin 250/500/750 mg tablets	Granulator, fluid bed dryer, sifter, tumbler, tablet press B, cota
Cetrizine tablets	Granulator, fluid bed dryer, sifter, tumbler, tablet press B, cota
Clarithromycin tablets	Granulator, fluid bed dryer, sifter, tumbler, tablet press B, cota
Metformin film-coated tablets	Granulator, fluid bed dryer, sifter, tumbler, tablet press B, cota
Lomefloxacin tablets	Granulator, fluid bed dryer, sifter, tumbler, tablet press B, cota
Acyclovir tablets	Granulator, fluid bed dryer, sifter, tumbler, tablet press B, cota
Attapulgite 150 mg tablets	Granulator, fluid bed dryer, sifter, tumbler, tablet press A, cota
Diclofenac 50 mg tablets	Granulator, fluid bed dryer, sifter, tumbler, tablet press B, cota
Bromhexine 8 mg tablets	Granulator, fluid bed dryer, sifter, tumbler, tablet press A, cota
Famotidine 200 mg tablets	Granulator, fluid bed dryer, sifter, tumbler, tablet press A, cota
Ciprofloxacin 500 tablets	Granulator, fluid bed dryer, sifter, tumbler, tablet press A, cota
Atenolol 100 mg tablets	Granulator, fluid bed dryer, sifter, tumbler, tablet press A, cota
Mebendazole tablets	Granulator, fluid bed dryer, sifter, tumbler, tablet press A, cota
Metronidazole tablets	Granulator, fluid bed dryer, sifter, tumbler, tablet press A, cota

18.1.3 Dry Granulation Uncoated Tablets

Product	Equipments
Prednisolone 20 mg tablets	Sifter, tumbler, tablet press A
Simethicone 42 mg tablets	Sifter, tumbler, tablet press A
Vitamin C 500 mg tablets	Sifter, tumbler, tablet press A
Aspirin 80 mg tablets	Sifter, tumbler, tablet press B
Metoclopramide 10 mg tablets	Sifter, tumbler, tablet press A/B
Pyridoxine 40 mg tablets	Sifter, tumbler, tablet press A
Folicron 5 mg tablets	Sifter, tumbler, tablet press A
Propranolol 40 mg tablets	Sifter, tumbler, tablet press A
Captopril tablets	Sifter, tumbler, tablet press A
Ranitidine 300 mg tablets	Sifter, tumbler, tablet press A
Multivitamin tablets	Sifter, tumbler, tablet press A

Your Company's Logo Your Company's Name

18.1.4 Dry Granulation Coated Tablets

Product	Equipments
B-complex tablets	Sifter, tumbler, tablet press A, cota
Ranitidine 300 mg tablets	Sifter, tumbler, tablet press A, cota
Multivitamin M tablets	Sifter, tumbler, tablet press A, cota

18.1.5 Sugar-Coated Tablets

Product	Equipments
Hyoscine S/C tableSts	Granulator, fluid bed dryer, sifter, tumbler, tablet press B, sugar-coating pan
Bisacodyl 5 mg tablets	Granulator, fluid bed dryer, sifter, tumbler, tablet press B, sugar-coating pan
Sennoside S/C tablets	Granulator, fluid bed dryer, sifter, tumbler, tablet press A, sugar-coating pan
Ibuprofen 200 mg tablets	Granulator, fluid bed dryer, sifter, tumbler, tablet press B, sugar-coating pan

In the above tables, products and the corresponding equipment train lists for tablets, manufactured in the ABC Pharmaceutical Company, were identified. Based on these matrices, the worst-case product for each piece of equipment will be chosen to conduct cleaning validation.

As discussed above, for each piece of equipment, more than one product will be chosen based on less solubility of excipients, high toxicity of APIs, and maximum therapeutic dose.

18.2 Product/Equipment Train (Capsules)

Product	Equipments
Indomethacin 25 mg	Sifter, encapsulator A
Tetracycline 250 mg	Sifter, encapsulator A
Oxytetracycline 250 mg	Sifter, encapsulator A
Doxycycline 100 mg	Sifter, encapsulator A
Fluoxitin	Sifter, encapsulator A
Azythromycin 250 mg	Sifter, encapsulator A
Oseltamivir 75 mg	Sifter, encapsulator A
Omeprazole 40 mg	Sifter, encapsulator B
Carbinoxamine	Sifter, encapsulator B
Erythromycin 250 mg	Sifter, encapsulator B
Lansoprazole 30 mg	Sifter, encapsulator B
Theophylline 300 mg	Sifter, encapsulator B
Folic acid/iron	Granulator, sifter, encapsulator B

Your Company's Logo

Your Company's Name

18.3 Product/Equipment Train (Granules)

Product	Equipments
Erythromycin 200 mg/mL	Granulator, fluid bed dryer, sifter, powder filling machine
Oseltamivir 12 mg/mL	Granulator, sifter, powder filling machine
Azythromycin 200 mg/5 mL	Granulator, sifter, powder filling machine

CLV-19

Worst-Case Products (Tablets, Capsules, and PPS) Matrix

Your Company's Logo **Your Company's Name**

In the previous chapter, we observed that equipment trains are used for manufacturing solid dosage forms, based on the respective processes. The objective of this protocol is to present an overview and the focus of discussion is to correlate the product's ingredients and the equipment train to select the worst-case product for each piece of equipment. It is always better to categorize and subcategorize the products in terms of the difference in processes to make the selection of worst-case products easy and simple: for example, products matrices based on coated or uncoated tablets or a matrix based on wet granulation or dry granulation products. Even if the same equipment is being used, there is no harm in selecting more than one worst-case product for one equipment train due to the difference in processes as explained above. The worst-case products for tablets, capsules, and PPS are presented in the following matrices.

19.1 Worst-Case Products (Tablets)

Products	Justification for Worst Case
Ciprofloxacin 500 tablet	Six ingredients insoluble in water
	Ciprofloxacin HCl (7)
	Kolidone (7)
	Primogel (7)
	Aerocil 200 (7)
	Magnesium stearate (7)
	Avicel PH-102 (7)
Ketotifen 1.0 mg tablets	Therapeutic dose 1.0 mg
Diclofenac 50 mg tablet	LD_{50} 150 mg/kg oral rat
B-complex tablets	Largest batch size (682 kg)

Your Company's Logo

Your Company's Name

19.1.1 For Coating Machines Only

Products	Justification for Worst Case
Ciprofloxacin 500 tablet	Six ingredients insoluble in water
Cetirizine 10 mg tablet	Less therapeutic dosage (10.0 mg)
Diclofenac 50 mg tablet	Toxicity. LD_{50} 150 mg/kg oral rat
B-complex tablets	Largest batch size (682 kg)

19.1.2 Sugar-Coated Products (for Conventional Coating Pans)

Products	Justification for Worst Case
Sennoside 12 mg tablets	Three ingredients insoluble in water
	Avicel (7)
	Magnesium stearate (7)
	Aerocil 200 (7)
Bisacodyl 5 mg tablets	Minimum therapeutic dose (5 mg)
Ibuprofen 200 mg	Largest batch size (495 kg)
Ibuprofen 200 mg	Toxicity. LD_{50} 636 mg/kg oral rat

After having done the selection of worst-case products for tablets based on product grouping and equipment train matrices, the same exercise will be carried out for all other products from various dosage forms, as shown in the following tables.

19.2 Worst-Case Products (Capsules)

19.2.1 For Encapsulator A

Products	Justification for Worst Case
Oxytetracycline	Three ingredients insoluble in water
	Aerocil 200 (7)
	Magnesium stearate (7)
	Talc fine (7)
Doxycycline 100 mg capsule	Maximum potency (100 mg)
Indomethacin 25 mg capsule	Largest batch size (1,000,000)

Your Company's Logo

Your Company's Name

19.2.2 For Encapsulator B

Products	Justification for Worst Case
Lansoprazole 30 mg capsule	Maximum potency (30 mg)
Erythromycin 250 mg capsule	Insoluble in water (7)
Folic acid/iron capsule	Largest batch size (1,000,000)

19.3 Worst-Case Products (Granules)

Products	Justification for Worst Case
Erythromycin 200 mg/5 mL	Two ingredients insoluble in water Erythromycin (7) Simethicone (7)
Azithromycin 200 mg	Second largest batch size (200.8 kg)

CLV-20

Validation with Corresponding Cleaning Procedures

Your Company's Logo **Your Company's Name**

In the tables given in the previous chapter, products and the corresponding equipment train lists for tablets, capsules, granules, suspensions, syrup, injectables and suppositories products, manufactured in ABC Pharmaceutical Company, were presented. Based on those matrices, the worst-case product for each piece of equipment was also chosen to conduct cleaning validation.

Basically, the Master Validation Plan is completed at this stage. The only thing remaining is to attach the schedule of all the validation activities to be carried out in the company. The validation professionals are to establish the schedule, maintain and update it on need basis.

Once all these prerequisites are identified, it is time to set about validating the procedures. The most significant document related with this event is the Validation protocol. Based on the information collected in the Master Validation Plan in the preceding chapters, and as per the worst-case products selected for each dosage form, we are presenting some generic protocols for the most commonly used equipments in the manufacturing areas.

The content of each protocol should be comprised of, as a minimum, scope, objective, responsibilities, cleaning procedure of the corresponding equipment, sampling plan, analytical methodology and acceptance criteria.

20.1 Protocols for Tablets Manufacturing Equipment

The worst-case products for tablets as identified in the Chapter 9, are as follows:

Products	Justification for Worst Case
Ciprofloxacin 500 mg tablets	*Six Ingredients non-soluble in water* Ciprofloxacin HCl (7) Kolidone (7) Primogel (7) Aerocil 200 (7) Magnesium stearate (7) Avicel PH-102 (7)
Ketotifen 1.0 mg tablets	Therapeutic dose 1.0 mg
Diclofenac 50 mg tablets	LD50 150 mg/kg oral rat
Sulphamethoxazole tablets	Largest batch size (682 kg)

The cleaning procedures for all the equipments used in the manufacturing of the four products given in the above table, will be validated as per this Master Validation Plan.

CLV-20.1

Cleaning Validation Protocol for Fluid Bed Dryer

Your Company's Logo

Your Company's Name

ABC Pharmaceutical Company	**CLEANING VALIDATION PROTOCOL** **Equipment Name**	
	Issued on **Date**	**Protocol Number** **CLVS 000**
	Location **Granulation Area** **Room No.000**	

Equipment ..... **Name of the Equipment**

Model ..... **XYZ**

Manufacturer ..... **Company Name and Country**

Written by	**Signature & Date**
Validation Officer	_____
Reviewed by	**Signature & Date**
QA Manager	_____
	Signature & Date
QC Manager	_____
	Signature & Date
Production Manager (Tablets)	_____
Approved by	**Signature & Date**
Production Director	_____
Authorized by	**Signature & Date**
QA Director	_____

Your Company's Logo **Your Company's Name**

20.1.1 Objective

The objective is to demonstrate that the cleaning procedure ABC-001 will successfully and consistently reduce the level of residues to a predetermined level of acceptability, so as to prevent contaminants (products or cleaning process related) from adversely affecting the safety and quality of the next product manufactured.

20.1.2 Scope

This protocol will cover cleaning validation of the fluid bed dryer used for the wet granulation of tablet products.

As per the MVP grouping matrix, products are divided into various groups based on their

a. Water solubility
b. Therapeutic dosage
c. Toxicity
d. Batch size (in kg)

From each group, one worst-case product is considered for cleaning validation. Table 20.1.1 lists the worst-case products for the fluid bed dryer (Figure 20.1.1).

20.1.3 Responsibility

The following personnel are responsible for the execution of this protocol:

Validation officer/QA officer/production officer/QA inspector/QC chemist/machine operator.

For details, please refer to Attachment II.

TABLE 20.1.1

Worst Case for Fluid Bed Dryer

Products	Reason for Selecting as Worst Case
Ciprofloxacin 500 mg tablets	Six ingredients are insoluble in water
Ketotifen 1.0 mg tablets	1.0 mg minimum therapeutic dose
Diclofenac 50 mg tablets	LD_{50}150 mg/kg oral rat
Sulfamethoxazole tablets	Largest batch size (682 kg)

Your Company's Logo **Your Company's Name**

FIGURE 20.1.1
Fluid bed dryer.

20.1.4 Description of the Cleaning Process

The fluid bed dryer is to be cleaned as per SOP No. ABC-001.

4.1 Fix "UNDER CLEANING" label
4.2 Wrap the electrical panel with a polythene sheet
4.3 Remove the bowl and dismantle the filter set
4.4 Soak the filter set in a 200-L drum filled with water overnight and then send it to laundry for washing and drying
4.5 Flush the bowl from both sides with water for 5 min
4.6 Clean the bowl with a nylon brush dipped in liquid soap
4.7 Flush the bowl with water for 3 min
4.8 Spray the bowl with 70% alcohol
4.9 Flush the fluid bed dryer from outside and inside and the filter basket and rinse with water for 5 min
4.10 Fix the filter set

4.11 Operate the fluid bed dryer as described in SOP No. ABC-002 for 1 h at 60°C to dry the filter set. Check the sleeves of the filter set for integrity
4.12 Clean the electrical panel and ducts with a wet towel
4.13 Remove accumulated water from the floor
4.14 Label the machine "CLEAN" as per site SOP
4.15 Make entries in the equipment cleaning, maintenance, and utilization logbook asper site SOP.

20.1.4.1 Difficult-to-Clean Parts

i. Filter set
ii. Inside bottom corner of the bowl
iii. Filter basket and ring

20.1.5 Description of the Sampling Process

20.1.5.1 Sampling Technique

The surface swab sampling technique will be used to take samples from the fluid bed dryer.

20.1.5.2 Sampling Precautions

Before taking the sample, wear

i. Gloves
ii. Face mask

Surface swabs (swabs with diluents including a suitable neutralizing agent)

20.1.5.3 Procedure for Sampling

20.1.5.3.1 Surface Swabs

Samples for the internal surfaces will be taken by moistening the swab (ready-made sterile cotton swab) with a suitable solvent (DIW). Sample a 25-cm^2 area (refer to Figures 20.1.2 through 20.1.7) and place the swab in a test tube containing 10 mL of a suitable solvent. Swab samples from each part of the fluid bed dryer will be collected as per Table 20.1.2.

Your Company's Logo **Your Company's Name**

TABLE 20.1.2

Surface Swabs Sampling Description

Description	Sample Location	Sample ID	Reference
Fluid bed dryer	Bowl bottom left edge	S1	Figure 20.1.2
	Bowl bottom center edge	S2	
	Bowl wall grove	S3	
	Bowl wall center	S4	
	Bowl bottom edge right	S5	
	Bowl wall right	S6	
	Bowl outer surface edge left	S7	Figure 20.1.3
	Bowl outer surface edge right	S8	
	Filter bottom surface left	S9	Figure 20.1.4
	Filter bottom surface center	S10	
	Filter bottom surface right	S11	
Fluid bed dryer	Dryer inside surface left	S12	Figure 20.1.5
	Dryer inside surface right	S13	
	Filter bags position 1	S14	Figure 20.1.6
	Filter bags position 2	S15	
	Filter bags position 3	S16	
	Dryer bottom surface left	S17	Figure 20.1.7
	Dryer bottom surface center	S18	
	Dryer bottom surface right	S19	

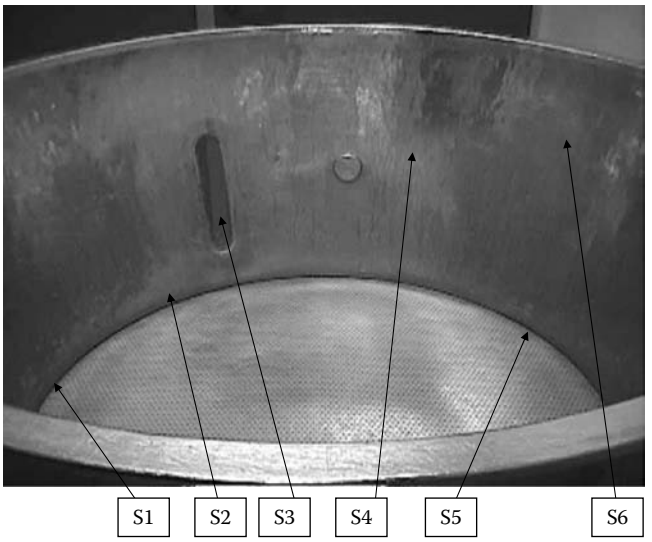


FIGURE 20.1.2
Bowl.

Your Company's Logo **Your Company's Name**

FIGURE 20.1.3
Bowl.

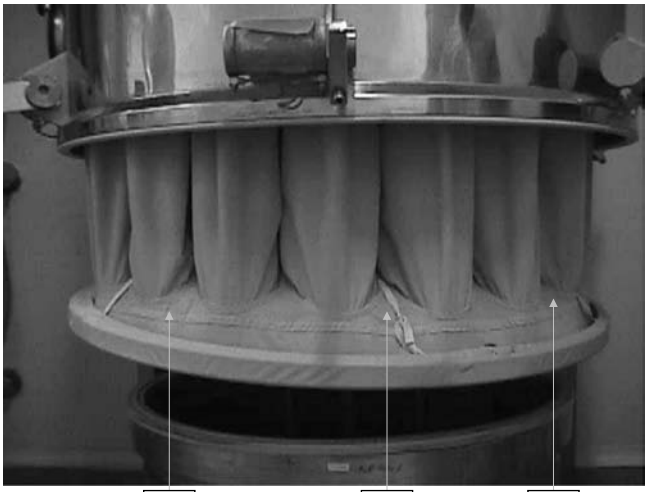


FIGURE 20.1.4
Bottom of the filter bags.

Your Company's Logo **Your Company's Name**

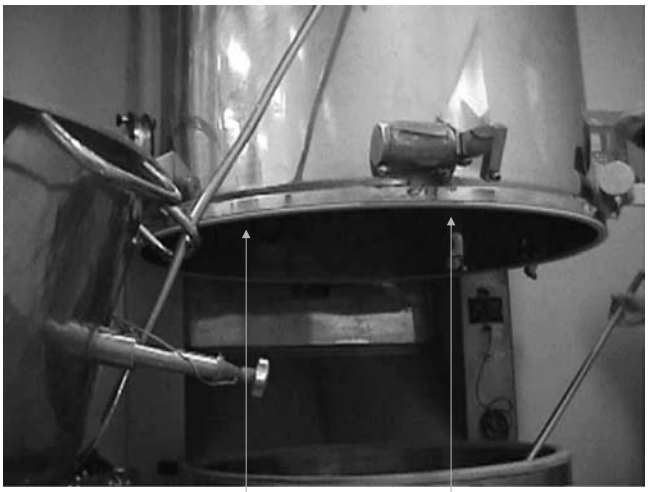


FIGURE 20.1.5
Inside wall.

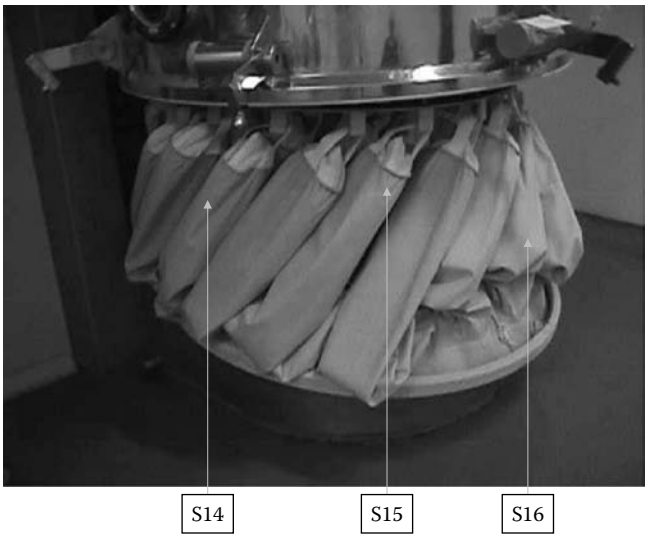


FIGURE 20.1.6
Outer surface of filter bags.

Your Company's Logo

Your Company's Name

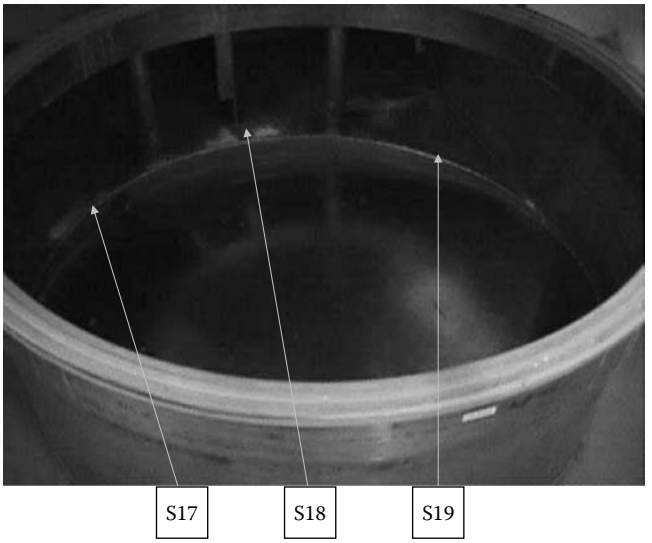


FIGURE 20.1.7
Inside surface of the lower part of fluid bed dryer.

20.1.5.4 Handling of Samples

i. The swabs samples collected for maximum allowable carryover (MAC) will be kept in the refrigerator.
ii. Analysis of swab samples on HPLC will be completed within 24 h after collection.
iii. HPLC samples should be kept at room temperature for at least 2 h before testing starts.

20.1.6 Test Functions

a. *Visual inspection:* Visual inspection of the fluid bed dryer will be performed as per SOP No. ABC-003.
b. *Maximum allowable carryover:* The test for MAC limits of the swab will be performed as per the HPLC method suitable for each product residue.

   Notes:

   - By pooling the 10 mL swab extraction for specific analysis, analysis will be carried out.
   - The validated HPLC test method will be used for the determination of chemical residues. Standard test method (STM) Nos are as follows:

c. *Bio-burden test:* The test for bio-burden will be performed as per STM No. MC-0001 by the QC Microbiology section.

d. *Swab recovery challenge test:* The swab recovery challenge test will be performed as per Parenteral Drug Association (PDA) *Journal of Pharmaceutical Science and Technology*.

e. *Detergent detection:* The test for detergent detection will be performed as per procedure ABC-004.

20.1.7 Verification of Documents

i. Verify the fluid bed dryer cleaning procedure.

ii. Verify the fluid bed dryer cleaning logbook records.

iii. Verify the cleaning operators and analyst training record (refer to Attachment V).

20.1.8 Documentation

i. All analysis results will be recorded in the analysis logbook.

ii. Printouts and chromatograms will be attached to the validation report and a copy of each will also be attached to the analytical logbook.

iii. All analysis and data have to be verified by a second analyst.

iv. The cleaning validation officer will check all training records.

v. The final report for cleaning validation will be prepared by the QA officer.

20.1.9 Acceptance Criteria

a. *Visual inspection:* The visible internal equipment surfaces and all critical and difficult-to-clean parts are optically free from residue and the color of the final rinse water is comparable to DIW.

b. *Maximum allowable carryover:* The active ingredient calculated (Z) is either equal to or less than the MAC.

$$Z \leq \text{MAC}$$

$$\text{MAC} = \frac{\text{TD} \times \text{BS} \times \text{SF}}{\text{LDD}}$$

Your Company's Logo **Your Company's Name**

where MAC is the maximum allowable carryover, TD is a single therapeutic dose, BS is the batch size of the next product to be manufactured in the same equipment, SF* is the safety factor (0.001), and LDD is the largest daily dose of the next product to be manufactured in the same equipment.

The calculated value will be the maximum amount of active ingredient of worst product that is allowed to be carried over to the next batch.

Calculation:

$$Y = X \times \text{surface area},$$

where Y is the active ingredient on the corresponding equipment part, X is the active ingredient recovered from 25 cm^2 by swab from the corresponding equipment part, and surface area is the area of the corresponding equipment parts A–S

$$Z = Y1 + Y2 + Y3 + Y4 + Y5 + Y6 + Y7 + Y8 + Y9 + Y10 + Y11 + Y12 + Y13 + Y14 + Y15 + Y16 + Y17 + Y18 + Y19,$$

where Z is the total active ingredient recovered from the machine, $Y1$ is the active ingredient recovered from part A, $Y2$ is the active ingredient recovered from part B, $Y3$ is the active ingredient recovered from part C, $Y4$ is the active ingredient recovered from part D, $Y5$ is the active ingredient recovered from part E, $Y6$ is the active ingredient recovered from part F, $Y7$ is the active ingredient recovered from part G, $Y8$ is the active ingredient recovered from part H, $Y9$ is the active ingredient recovered from part I, $Y10$ is the active ingredient recovered from part J, $Y11$ is the active ingredient recovered from part K, $Y12$ is the active ingredient recovered from part L, $Y13$ is the active ingredient recovered from part M, $Y14$ is the active ingredient recovered from part N, $Y15$ is the active ingredient recovered from part O, $Y16$ is the active ingredient recovered from part P, $Y17$ is the active ingredient recovered from part Q, $Y18$ is the active ingredient recovered from part R, and $Y19$ is the active ingredient recovered from part S.

Acceptance criteria:

$$Z \leq \text{MAC}.$$

c. *Bio-burden:* The bio-Burden should not be more than 33 cfu/25 cm^2 for the swabs.
d. *Swab recovery challenge test:* The swab recovery challenge test should be NLT 70% of the known concentration of standard spiked.
e. *Detergent detection:* No foam was detected on the top of the sample after testing.

* 1/100 to 1/1000 of a normal daily dose for oral products (PDA Guideline).

Your Company's Logo **Your Company's Name**

20.1.10 List of Attachments

Attachment I	Description of equipment and product
Attachment II	Cleaning/testing responsibilities
Attachment III	Sampling and testing plan
Attachment IV	Calculations for surface swabs
Attachment V	Training record verification
Attachment VI	Swabs analysis results
Attachment VII	Swab sampling recovery challenge test results

Your Company's Logo **Your Company's Name**

Attachment I

Description of Equipment and Product

Equipment Name: _____

Serial No.: _____

Capacity: _____

Calibrated on: _____

Validated on: _____

Location: _____

Room No.: _____

Previous Product: _____

B. No. of the Product: _____

Worst-Case Products

- ☐ Ciprofloxacin tablet 500 mg
- ☐ Ketotifen tablet 1.0 mg
- ☐ Diclofenac 50 mg tablets
- ☐ Sulfamethoxazole tablets

Next Product to Be Manufactured in the Same Equipment: _____

Manufacturing Date: _____

Active Ingredient: _____

Therapeutic Group: _____

Cleaning Date: _____

Cleaning SOP No. _____ Revision No. _____

Sampling Technique: _____ Test Method Reference: _____

Cleaning Sample Analysis Date/Time: _____ Result: _____

Limit of Detection: _____ Reference Analytical Logbook: _____

Safety Factor: _____

Your Company's Logo **Your Company's Name**

Attachment II

Worst-Case Products

- ☐ Ciprofloxacin tablet 500 mg
- ☐ Ketotifen tablet 1.0 mg
- ☐ Diclofenac 50 mg tablets
- ☐ Sulfamethoxazole tablets

Cleaning/Testing Responsibilities

Cleaning/Testing	Done By	Recorded On	Checked By
Equipment cleaning	Machine operator	Equipment usage/ cleaning logbook	Production supervisor
Visual inspection	Validation officer	Analytical logbook	—
Swab sample	Machine operator/ validation officer	Sampling sheet	Validation officer
Detergent determination	Validation officer/QC analyst	Analytical logbook	QA/QC officer
MAC	Validation officer/QC analyst	Analytical logbook	*QC* officer
Bio-burden	Microbiologist	Analytical logbook	QC assistant manager, microbiology
Swab recovery challenge test	Analyst	Analytical logbook	Senior analyst

Your Company's Logo **Your Company's Name**

Attachment III

Worst-Case Products

- ☐ Ciprofloxacin tablet 500 mg
- ☐ Ketotifen tablet 1.0 mg
- ☐ Diclofenac 50 mg tablets
- ☐ Sulfamethoxazole tablets

Sampling and Testing Plan

S. No.	Visual Inspection	Detergent Detection	Identification Labeling	Sample Area (cm^2)	Surface Area (cm^2)	MAC	Less Than or Equal to Limit of Detection	Bio-Burden NMT 33 cfu/swab	Testing Method
1.			S1	25	3333				STM-MC-001
2.			S2	25	3333				
3.			S3	25	3360				
4.			S4	25	3360				
5.			S5	25	3333				
6.			S6	25	3360				
7.			S7	25	5040				
8.			S8	25	5040				
9.			S9	25	15,833				
10.			S10	25	15,833				
11.			S11	25	15,833				
12.			S12	25	5000				
13.			S13	25	5000				
14.			S14	25	15,833				
15.			S15	25	15,833				
16.			S16	25	15,833				
17.			S17	25	3333				
18.			S18	25	3333				
19.			S19	25	3333				

Your Company's Logo **Your Company's Name**

Attachment IV

Worst-Case Products

- ☐ Ciprofloxacin tablet 500 mg
- ☐ Ketotifen tablet 1.0 mg
- ☐ Diclofenac 50 mg tablets
- ☐ Sulfamethoxazole tablets

Calculation for Surface Swabs

$$\text{MAC} = \frac{\text{TD} \times \text{BS} \times \text{SF}}{\text{LDD}}$$

Calculation:

$$Y = X \times \text{surface area},$$

where Y is the active ingredient on the corresponding equipment part, X is the active ingredient recovered from 25 cm^2 by swab from the corresponding equipment part, and surface area is the area of the corresponding equipment parts A–S.

$$Z = Y1 + Y2 + Y3 + Y4 + Y5 + Y6 + Y7 + Y8 + Y9 + Y10 + Y11 + Y12 + Y13 + Y14 + Y15 + Y16 + Y17 + Y18 + Y19,$$

where Z is the total active ingredient recovered from machine, $Y1$ is the active ingredient recovered from part S1, $Y2$ is the active ingredient recovered from part S2, $Y3$ is the active ingredient recovered from part S3, $Y4$ is the active ingredient recovered from part S4, $Y5$ is the active ingredient recovered from part S11, $Y6$ is the active ingredient recovered from part S12, $Y7$ is the active ingredient recovered from part S13, $Y8$ is the active ingredient recovered from part S14, $Y9$ is the active ingredient recovered from part S5, $Y10$ is the active ingredient recovered from part S15, $Y11$ is the active ingredient recovered from part S6, $Y12$ is the active ingredient recovered from part S7, $Y13$ is the active ingredient recovered from part S8, $Y14$ is the active ingredient recovered from part S9, $Y15$ is the active ingredient recovered from part S10, $Y16$ is the active ingredient recovered from part S16, $Y17$ is the active ingredient recovered from part S17, $Y18$ is the active ingredient recovered from part S18, and $Y19$ is the active ingredient recovered from part S19.

Acceptance criteria:

$$Z \leq \text{MAC}.$$

Your Company's Logo **Your Company's Name**

Attachment V

Worst-Case Products

- ☐ Ciprofloxacin tablet 500 mg
- ☐ Ketotifen tablet 1.0 mg
- ☐ Diclofenac 50 mg tablets
- ☐ Sulfamethoxazole tablets

Training Record Verification (Production Staff)

The following staff found trained on cleaning of the equipment.

Using SOP No. ABC-006; Revision No; Issued on; Date

Name: _____ ID No. _____ Sign. _____ Date _____

Name: _____ ID No. _____ Sign. _____ Date _____

Training Record Verification (Analyst)

The following analyst trained on STM No. _____

Name: _____ ID No. _____ Sign. _____ Date _____

Performed by: _____ Checked by: _____

Date: _____ Date: _____

Your Company's Logo **Your Company's Name**

Attachment VI

Worst-Case Products

- ☐ Ciprofloxacin tablet 500 mg
- ☐ Ketotifen tablet 1.0 mg
- ☐ Diclofenac 50 mg tablets
- ☐ Sulfamethoxazole tablets

Swab Analysis Results

Sampling Location	Visual Inspection	Detergent Detection	Bio-Burden Test NMT 33 cfu/swab	Carryover HPLC Result per 25 cm^2 (X)	Carryover 25 cm^2 × Surface Area Total Carryover $Y = X \times (A–S)$
S1					
S2					
S3					
S4					
S5					
S6					
S7					
S8					
S9					
S10					
S11					
S12					
S13					
S14					
S15					
S16					
S17					
S18					
S19					

Your Company's Logo **Your Company's Name**

Attachment VII

Swab Sampling Recovery (Challenge) Test

Name of Active Material	Concentration of Standard Solution	Type of Swab	Total Area of Swab	% Recovery of Active Ingredient	% Recovery as per Limit NLT (70%)	
					Y	N

CLV-20.2

Cleaning Validation Protocol for Mixer

Your Company's Logo

Your Company's Name

ABC Pharmaceutical Company	**CLEANING VALIDATION PROTOCOL** **Equipment Name**	
	Issued on **Date**	**Protocol Number** **CLVS 000**
	Location **Granulation Area** **Room No.000**	

Equipment ..... **Equipment Name**

Model ..... **Model/Number**

Manufacturer ..... **Name and Country**

Written by	**Signature & Date**
Validation Officer	_____
Reviewed by	**Signature & Date**
QA Manager	_____
	Signature & Date
QC Manager	_____
	Signature & Date
Production Manager	_____
Approved by	**Signature & Date**
Production Director	_____
Authorized by	**Signature & Date**
QA Director	_____

Your Company's Logo **Your Company's Name**

20.2.1 Objective

The objective is to demonstrate that the cleaning procedure No. ABC-001 will successfully and consistently reduce the level of residues to a predetermined level of acceptability, so as to prevent contamination (product or cleaning process related) from adversely affecting the safety and quality of the next product manufactured.

20.2.2 Scope

This protocol will cover cleaning of the mixer for tablet products.

As per CVMP grouping matrix, products are divided into various groups based on their

a. Water solubility
b. Therapeutic dosage
c. Toxicity
d. Batch size (in kg)

From each group one worst-case product is considered for cleaning validation (Table 20.2.1) of the Mixer (Figure 20.2.1).

20.2.3 Responsibility

The following personnel are responsible for the execution of this protocol:

Validation officer/production officer/QA inspector/QC chemist/machine operator.

For details, please refer to Attachment II.

TABLE 20.2.1

Worst Case for the Mixer

Products	Reason for Selecting as Worst Case
Ciprofloxacin 500 mg tablets	Six ingredients are insoluble in water
Ketotifen 1.0 mg tablets	Minimum therapeutic dose (1.0 mg)
Diclofenac 50 mg tablets	LD_{50}150 mg/kg oral rat
Sulfamethoxazole 20 mg tablets	Largest batch size (1000 kg)

Your Company's Logo **Your Company's Name**

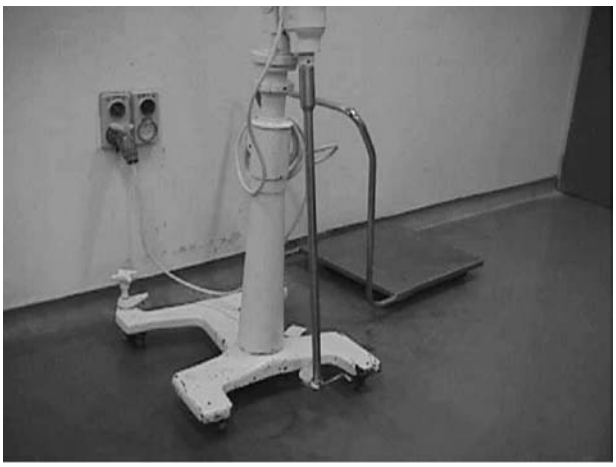


FIGURE 20.2.1
Mixer with stand.

20.2.4 Description of the Cleaning Process

The mixer is to be cleaned manually as per SOP No. ABC-001.

4.1 Label the equipment "UNDER CLEANING" as per SOP No. ABC-002
4.2 Disconnect the power supply by removing the plug out from the socket
4.3 Clean the impeller, shaft motor, and stand using soft sponge soaked in 1% detergent solution
4.4 Flush the shaft, impeller, and stand with 10 L of water using a 1 L jug
4.5 Wipe up the motor and stand with a cotton cloth soaked in 70% alcohol
4.6 After sanitation, cover the stirrer rod with a clean polybag up to half-length
4.7 Label the mixer "CLEAN"

20.2.4.1 Difficult-to-Clean Parts

i. Impeller
ii. Shaft

20.2.5 Description of the Sampling Process

20.2.5.1 Sampling Technique

The surface swab sampling technique will be used to take the sample from the mixer.

Your Company's Logo **Your Company's Name**

FIGURE 20.2.2
Mixer.

20.2.5.2 Sampling Precautions

Before taking the samples, wear

i. Gloves
ii. Face mask

20.2.5.3 Procedure for Sampling

Samples for the internal surfaces will be taken by moistening the swab (ready-made sterile cotton swab) with a suitable solvent (DIW/alcohol–water–alcohol). Sample a 25-cm^2 area (see Figure 20.2.2) and place the swab in a test tube containing 10 mL of solvent (suitable solvent). The swab sample from each part of the mixer will be collected as per Table 20.2.2.

TABLE 20.2.2
Surface Swabs Sampling Description

Description	Sample Location	Sample ID	Reference
Mixer	Impeller 1	S1	Figure 20.2.2
	Impeller 2	S2	
	Impeller 3	S3	
	Shaft bottom	S4	
	Shaft top	S5	

Your Company's Logo Your Company's Name

20.2.5.4 Handling of Samples

i. After collecting swab samples for MAC, they are kept in the refrigerator.
ii. Swab samples for the HPLC analysis were collected at the time of manufacturing; analysis should be completed within 24 h after collection.
iii. HPLC samples should be kept at room temperature for at least 2 h before testing.

20.2.6 Test Functions

a. *Visual inspection:* Inspection of the mixer will be performed visually at the end of the cleaning procedure.
b. *Maximum allowable carryover:* The test for MAC of the final rinse/swab will be performed as per the HPLC method suitable for each product residue.

   Notes:

   - By pooling the 10 mL swab extraction for specific analysis, analysis will be carried out.
   - The validated HPLC test method will be used for the determination of chemical residues.

c. *Bio-burden test:* The test for bio-burden will be performed as per STM No. MC-0001, by QC Microbiology section.
d. *Swab recovery challenge test:* The recovery challenge test of the swab sample will be performed as per PDA *Journal of Pharmaceutical Science and Technology*.
e. *Detergent detection:* The test for the detergent detection will be performed as per the procedure No. ABC-003.

20.2.7 Verification of Documents

i. Verify the mixer cleaning procedure
ii. Verify the mixer cleaning logbook records
iii. Verify the cleaning operators and the analyst training record (refer to Attachment V)

20.2.8 Documentation

i. All analysis results will be recorded in the analysis logbook.
ii. Printouts and chromatograms will be attached to the validation report and a copy of that is also attached to the analytical logbook.

Your Company's Logo Your Company's Name

iii. A second analyst will verify all analyses and data.
iv. A quality assurance officer will check all training records.
v. The final report for cleaning validation will be prepared by the QA officer.

20.2.9 Acceptance Criteria

a. *Visual inspection:* The visible internal equipment surfaces and all critical and difficult-to-clean parts are optically free from residue and the color of the final rinse water is comparable to DIW.
b. *Maximum allowable carryover:* The active ingredient calculated (*Z*) is either equal to or less than the MAC.

$$Z \leq \text{MAC}$$

$$\text{MAC} = \frac{\text{TD} \times \text{BS} \times \text{SF}}{\text{LDD}},$$

where MAC is the maximum allowable carryover, TD is the a single therapeutic dose, BS is the batch size of the next product to be manufactured in the same equipment, SF* is the safety factor (0.001), and LDD is the largest daily dose of the next product to be manufactured in the same equipment.

The calculated value will be the maximum amount of active ingredient of worst-case product that is allowed to be carried over to the next batch.

Calculation:

$$Y = X \times \text{surface area},$$

where *Y* is the active ingredient on the corresponding equipment part, *X* is the active ingredient recovered from 25 cm^2 by swab from the corresponding equipment part, and surface Area is the area of the corresponding equipment parts A–E.

$$Z = Y1 + Y2 + Y3 + Y4 + Y5,$$

where *Z* is the total active ingredient recovered from the machine, *Y*1 is the active ingredient recovered from part S1, *Y*2 is the active ingredient recovered from part S2, *Y*3 is the active ingredient recovered from part S3, *Y*4 is the active ingredient recovered from part S4, and *Y*5 is the active ingredient recovered from part S5.

* 1/100 to 1/1000 of a normal daily dose for oral products (PDA Guideline).

Your Company's Logo **Your Company's Name**

Acceptance criteria:

$$Z \leq \text{MAC}.$$

c. *Bio-burden:* The bio-burden should not be more than 33 cfu/25 cm^2 for the swabs.

d. *Swab recovery challenge test:* The swab recovery challenge test should be NLT 70% of the known concentration of standard spiked.

e. *Detergent detection:* No foam was detected on top of the rinse sample after testing.

20.2.10 List of Attachments

Attachment I	Description of equipment and product
Attachment II	Cleaning/testing responsibilities
Attachment III	Sampling and testing plan
Attachment IV	Calculations for surface swabs
Attachment V	Training record verification
Attachment VI	Swabs analysis results
Attachment VII	Swab sampling recovery challenge test results

Your Company's Logo **Your Company's Name**

Attachment I

Description of Equipment and Product

Equipment Name: _____

Serial No.: _____

Capacity: _____

Room No.: _____

Product Name: _____

Worst-Case Products

- ☐ Ciprofloxacin 500 mg tablets
- ☐ Ketotifen 1.0 mg tablets
- ☐ Diclofenac 50 mg tablets
- ☐ Sulfamethoxazole D/S tablets

Batch No. of the Product: _____

Next Product to Be Manufactured in the Same Equipment: _____

Manufacturing Date: _____

Active Ingredient: _____

Therapeutic Group: _____

Cleaning Date: _____

Cleaning SOP No.: _____ Revision No.: _____

Sampling Technique: _____

Cleaning Sample Analysis Date/Time: _____ Result: _____

Test Method Reference: _____ Reference Analytical Logbook: _____

Limit of Detection: _____

Safety Factor: _____

Your Company's Logo **Your Company's Name**

Attachment II

Worst-Case Products

- ☐ Ciprofloxacin 500 mg tablets
- ☐ Ketotifen 1.0 mg tablets
- ☐ Diclofenac 50 mg tablets
- ☐ Sulfamethoxazole D/S tablets

Cleaning/Testing Responsibilities

Cleaning/Testing	Done by	Recorded on	Checked by
Equipment cleaning	Machine operator	Equipment usage/ cleaning logbook	Production supervisor
Visual inspection	Validation officer	Analytical logbook	—
Swab sample	Machine operator/validation officer	Sampling sheet	—
Detergent	Validation officer/QC analyst	Analytical logbook	QA/QC officer
MAC	Validation officer/QC analyst	Analytical logbook	Validation officer
Bio-burden	Microbiologist	Analytical logbook	Manager QC, microbiology
Swab recovery challenge test	QC analyst	Analytical logbook	Senior analyst

Your Company's Logo **Your Company's Name**

Attachment III

Worst-Case Products

- ☐ Ciprofloxacin 500 mg tablets
- ☐ Ketotifen 1.0 mg tablets
- ☐ Diclofenac 50 mg tablets
- ☐ Sulfamethoxazole D/S tablets

Sampling and Testing Plan

S. No.	Visual Inspection	Detergent Detection	Identification Labeling	Sample Area (cm^2)	Surface Area (cm^2)	MAC	Less than or Equal to Limit of Detection	Bio-Burden NMT33cfu/ 2.5 cm^2	Testing Method
			S1	25	1000				STM-MC-0001
			S2	25	1000				
			S3	25	1000				
			S4	25	1000				
			S5	25	1000				

Performed by: _____ Checked by: _____

Date: _____ Date: _____

Your Company's Logo **Your Company's Name**

Attachment IV

Worst-Case Products

- ☐ Ciprofloxacin 500 mg tablets
- ☐ Ketotifen 1.0 mg tablets
- ☐ Diclofenac 50 mg tablets
- ☐ Sulfamethoxazole D/S tablets

Calculation for Surface Swabs

$$\text{MAC} = \frac{\text{TD} \times \text{BS} \times \text{SF}}{\text{LDD}}$$

Calculation:

$$Y = X \times \text{surface area},$$

where Y is the active ingredient on the corresponding equipment part, X is the active ingredient recovered from a 25 cm^2 by swab from the corresponding equipment part, and surface area is the area of the corresponding equipment parts A–E.

$$Z = Y1 + Y2 + Y3 + Y4 + Y5,$$

where Z is the total active ingredient recovered from the machine, $Y1$ is the active ingredient recovered from part S1, $Y2$ is the active ingredient recovered from part S2, $Y3$ is the active ingredient recovered from part S3, $Y4$ is the active ingredient recovered from part S4, and $Y5$ is the active ingredient recovered from part S5.

Acceptance criteria:

$$Z \leq \text{MAC}.$$

Your Company's Logo **Your Company's Name**

Attachment V

Worst-Case Products

- ☐ Ciprofloxacin 500 mg tablets
- ☐ Ketotifen 1.0 mg tablets
- ☐ Diclofenac 50 mg tablets
- ☐ Sulfamethoxazole D/S tablets

Training Record Verification (Production Staff)

The following staff found trained on cleaning of the equipment.

Using SOP No. ABC-006; Revision No; Issued on; Date

Name: _____ ID No. _____ Sign. _____ Date _____

Name: _____ ID No. _____ Sign. _____ Date _____

Training Record Verification (Analyst)

The following analyst trained on STM No. _____

Name: _____ ID No. _____ Sign. _____ Date _____

Performed by: _____ Checked by: _____

Date: _____ Date: _____

Your Company's Logo **Your Company's Name**

Attachment VI

Worst-Case Products

- ☐ Ciprofloxacin 500 mg tablets
- ☐ Ketotifen 1.0 mg tablets
- ☐ Diclofenac 50 mg tablets
- ☐ Sulfamethoxazole D/S tablets

Swab Analysis Results

Sampling Location	Visual Inspection	Detergent Detection	Bio-Burden Test NMT 33 cfu/25 cm^2	Carryover HPLC Result per 25 cm^2 (X)	Carryover 25 cm^2 × Surface Area Total Carryover $Y = X \times (A - E)$
S1					
S2					
S3					
S4					
S5					

Your Company's Logo **Your Company's Name**

Attachment VII

Swab Sampling Recovery (Challenge) Test

Name of Active Material	Concentration of Standard Solution	Type of Swab	Total Area of Swab	% Recovery of Active Ingredient	% Recovery as per Limit NLT (70%)	
					Y	N

CLV-20.3

Cleaning Validation Protocol for Granulation Machines (Type A)

Your Company's Logo

Your Company's Name

ABC Pharmaceutical Company	**CLEANING VALIDATION PROTOCOL** **Equipment Name**	
	Issued on **Date**	**Protocol Number** **CLVS 000**
	Location **Granulation Area** **Room No.000**	

Equipment ..... **Granulation Machine Type A**

Model ..... **Model**

Manufacturer ..... **Company, Country**

Written by	**Signature & Date**
Validation Officer	_____
Reviewed by	**Signature & Date**
QA Manager	_____
	Signature & Date
QC Manager	_____
	Signature & Date
Production Manager	_____
Approved by	**Signature & Date**
Production Director	_____
Authorized by	**Signature & Date**
QA Director	_____

Your Company's Logo **Your Company's Name**

20.3.1 Objective

The objective is to demonstrate that the cleaning procedure No. ABC-001 will successfully and consistently reduce the level of residues to a predetermined level of acceptability, so as to prevent contamination (product or cleaning process related) from adversely affecting the safety and quality of the next product manufactured.

20.3.2 Scope

This protocol will cover cleaning of the granulation machine used for the tablet products. As per CVMP grouping matrix, products are divided into various groups based on their

a. Water solubility
b. Therapeutic dosage
c. Toxicity
d. Batch size (in kg)

From each group one worst-case product is considered for cleaning validation (Table 20.3.1).

20.3.3 Responsibility

The following personnel are responsible for the execution of this protocol:

Validation officer/production officer/QA inspector/QC chemist/machine operator.

For details, please refer to Attachment II.

TABLE 20.3.1

Worst-Case Products for Granulation Machine

Products	Reason for Selecting as Worst Case
Ciprofloxacin 500 mg tablets	Six ingredients are in soluble in water
Ketotifen 1.0 mg tablets	Minimum therapeutic dose (1.0 mg)
Diclofenac 50 mg tablets	LD_{50} 150 mg/kg oral rat
Sulfamethoxazole D/S tablets	Largest batch size (825 kg)

Your Company's Logo **Your Company's Name**

20.3.4 Description of the Cleaning Process

The granulation machine will be cleaned manually as per SOP No. ABC-001.

4.1 Remove the "UNDER CLEANING" label
4.2 Dismantle the rotor of each machine
4.3 Take out the sieve from each machine
4.4 Take out the sieve holder bars, and deflectors
4.5 Dismantle the rigid screen-support
4.6 Clean the sieve as per SOP No. ABC-002
4.7 Flush the dismantle parts with water and clean each part with a sponge dipped in liquid soap
4.8 Flush the dismantled parts with water for 2 min
4.9 Place a 200-L stainless steel drum under the machines
4.10 Flush the inside of the machines with water for 1 min
4.11 Clean the inside of the machines with a sponge dipped in liquid soap
4.12 Flush the inside of the machines with water for 2 min
4.13 Clean the outside of the machine with a wet clean towel
4.14 Spray the dismantle parts and the inside of the machines with 70% alcohol
4.15 Assemble the parts to the machine
4.16 Label the machine "CLEAN"
4.17 Make entries in the equipment cleaning, maintenance, and production logbook as per SOP

20.3.4.1 Difficult-to-Clean Parts

i. Sieve
ii. Sieve holder bars

20.3.5 Description of the Sampling Process

20.3.5.1 Sampling Technique

The surface swab sampling technique will be used to take samples from the granulation machine.

Your Company's Logo **Your Company's Name**

TABLE 20.3.2

Surface Swabs Sampling Description

Description	Sample Location	Sample ID	Reference
Granulation machine	Powder loading surface	S1	Figure 20.3.1
	Granulator surface	S2	
	Outlet surface of bowl	S3	
	Granulator surface left	S4	Figure 20.3.2
	Granulator surface center	S5	
	Bowl outlet surface left	S6	Figure 20.3.3
	Bowl outlet surface center	S7	
	Bowl outlet surface right	S8	
	Sieve	S9	

20.3.5.2 Sampling Precautions

Before taking the sample, wear

i. Gloves
ii. Face mask

20.3.5.3 Procedure for Sampling

Samples for the internal surfaces will be taken by moistening the swab (ready-made sterile cotton swab) with a suitable solvent (deionized water/alcohol–water–alcohol). Sample a 25-cm^2 area (see Figures 20.3.1 through 20.3.3) and place the swab in a test tube containing 10 mL of solvent (suitable solvent). Swab samples from each part of the granulation machine will be collected as per Table 20.2.2.

20.3.5.4 Handling of Samples

i. After collecting swab samples for MAC, they are kept in the refrigerator.
ii. HPLC samples should be kept at room temperature for at least 2 h before testing starts.

20.3.6 Test Functions

a. *Visual inspection:* Inspection of the granulation machine will be performed visually, after the cleaning procedure.

Your Company's Logo **Your Company's Name**

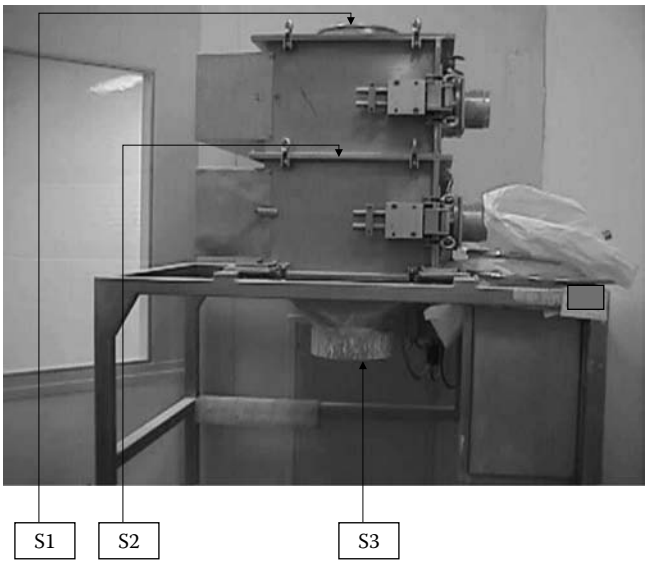


FIGURE 20.3.1
Granulator type A.

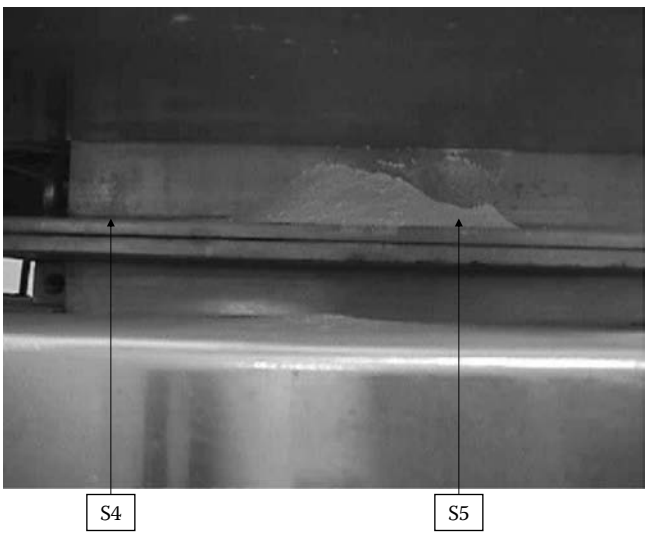


FIGURE 20.3.2
Outer surface of the granulator.

Your Company's Logo **Your Company's Name**

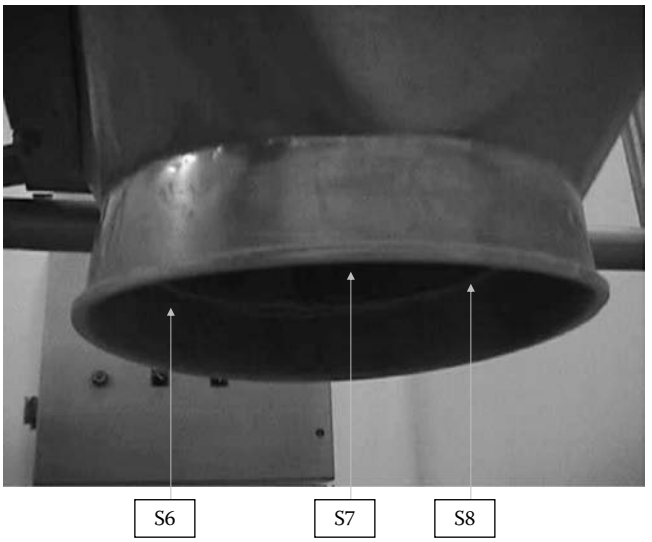


FIGURE 20.3.3
Opening of the granulator.

b. *Maximum allowable carryover:* The test for MAC of the final swab will be performed as per the HPLC method suitable for each product residue.

   Notes:

   - By pooling the 10 mL swab extraction for specific analysis, analysis will be carried out.
   - The validated HPLC test method will be used for the determination of chemical residues.

c. *Bio-burden test:* The test for bio-burden will be performed as per STM No. MC-0001, by QC Microbiology section.

d. *Swab recovery challenge test:* The recovery challenge test will be performed of the swab sample as per PDA *Journal of Pharmaceutical Science and Technology*.

e. *Detergent detection:* The test for the detergent detection will be performed as per procedure No. ABC-003.

20.3.7 Verification of Documents

i. Verify the granulation machine cleaning procedure
ii. Verify the granulation machine cleaning logbook records
iii. Verify the cleaning operator and analyst training record (refer to Attachment V)

Your Company's Logo **Your Company's Name**

20.3.8 Documentation

i. All analysis results will be recorded in the analysis logbook.
ii. Printouts and chromatograms will be attached to the validation report and a copy of that is also attached to the analytical logbook.
iii. A second analyst will verify all analyses and data.
iv. A cleaning validation officer will check all training records.
v. The final report for cleaning validation will be prepared by the QA officer.

20.3.9 Acceptance Criteria

a. *Visual inspection:* The visible internal equipment surfaces and all critical and difficult-to-clean parts are optically free from residue and the color of the final rinse water is comparable to DIW.
b. *Maximum allowable carryover:* The active ingredient calculated (Z) is either equal to or less than the MAC. Based on the "worst-case" concept,

$$Z \leq \text{MAC}.$$

$$\text{MAC} = \frac{\text{TD} \times \text{BS} \times \text{SF}}{\text{LDD}},$$

where MAC is the maximum allowable carryover, TD is a single therapeutic dose, BS is the batch size of the next product to be manufactured in the same equipment, SF* is the safety factor (0.001), and LDD is the largest daily dose of the next product to be manufactured in the same equipment.

The calculated value will be the maximum amount of active ingredient of worst-case product that is allowed to be carried over to the next batch.

Calculation:

$$Y = X \times \text{surface area},$$

where Y is the active ingredient on the corresponding equipment part, X is the active ingredient recovered from 25 cm^2 by swab from the corresponding equipment part, and surface area is the area of the corresponding equipment parts A to I.

$$Z = Y1 + Y2 + Y3 + Y4 + Y5 + Y6 + Y7 + S8 + S9,$$

* 1/100 to 1/1000 of a normal daily dose for oral products (PDA Guideline).

where Z is the total active ingredient recovered from the machine, $Y1$ is the active ingredient recovered from part S1, $Y2$ is the active ingredient recovered from part S2, $Y3$ is the active ingredient recovered from part S3, $Y4$ is the active ingredient recovered from part S4, $Y5$ is the active ingredient recovered from part S5, $Y6$ is the active ingredient recovered from part S6, $Y7$ is the active ingredient recovered from part S7, and $Y8$ is the active ingredient recovered from part S8.

Acceptance criteria:

$$Z \leq \text{MAC}.$$

c. *Bio-burden:* The bio-burden should not be more than 33 cfu/25 cm^2 for the swabs.
d. *Swab recovery challenge test:* The swab recovery challenge test should be 70% of the known concentration of standard spiked.
e. *Detergent detection:* No foam was detected on top of the sample after testing.

20.3.10 List of Attachments

Attachment I	Description of equipment and product
Attachment II	Cleaning/testing responsibilities
Attachment III	Sampling and testing plan
Attachment IV	Calculations for surface swabs
Attachment V	Training record verification
Attachment VI	Swabs analysis results
Attachment VII	Swab sampling recovery challenge test results

Your Company's Logo **Your Company's Name**

Attachment I

Description of Equipment and Product

Equipment Name: _____

Serial No.: _____

Location: _____

Room No.: _____

Product Name: _____

Batch No. of the Product: _____

Worst-Case Products

- ☐ Ciprofloxacin tablet 500 mg
- ☐ Diclofenac tablet 50 mg
- ☐ Ketotifen 1.0 mg tablets
- ☐ Sulfamethoxazole DS tablets

Next Product to Be Manufactured in the Same Equipment: _____

Manufacturing Date: _____

Active Ingredient: _____

Therapeutic Group: _____

Cleaning Date: _____

Cleaning SOP No.: _____ Revision No.: _____

Sampling Technique: _____

Cleaning Sample Analysis Date/Time: _____ Result: _____

Test Method Reference: _____ Reference Analytical Logbook: _____

Limit of Detection: _____

Safety Factor: _____

Your Company's Logo **Your Company's Name**

Attachment II

Worst-Case Products

- ☐ Ciprofloxacin tablet 500 mg
- ☐ Diclofenac tablet 50 mg
- ☐ Ketotifen 1.0 mg tablets
- ☐ Sulfamethoxazole DS tablets

Cleaning/Testing Responsibilities

Cleaning/Testing	Done by	Recorded on	Checked by
Equipment cleaning	Machine operator	Equipment usage/ cleaning logbook	Production supervisor
Visual inspection	Validation officer	Analytical logbook	—
Swab sample	Machine operator/validation officer	Sampling sheet	—
Detergent determination	Validation officer/QC analyst	Analytical logbook	QA/QC officer
MAC	Validation officer/QC analyst	Analytical logbook	QC officer
Bio-burden	Microbiologist	Analytical logbook	QC manager, microbiology
Swab recovery challenge test	Analyst	Analytical logbook	Senior analyst

Your Company's Logo **Your Company's Name**

Attachment III

Worst-Case Products

- ☐ Ciprofloxacin tablet 500 mg
- ☐ Diclofenac tablet 50 mg
- ☐ Ketotifen 1.0 mg tablets
- ☐ Sulfamethoxazole DS tablets

Sampling and Testing Plan

S. No.	Visual Inspection	Identification Labeling	Sample Area (cm^2)	Surface Area in Contact with Product (cm^2)	Detergent Test	MAC	Bio-Burden NMT 33 cfu/25 cm^2	Testing Method
1.		S1	25	2205				
2.		S2	25	2205				
3.		S3	25	225				
4.		S4	25	662				
5.		S5	25	662				
6.		S6	25	225				
7.		S7	25	225				
8.		S8	25	225				

Your Company's Logo **Your Company's Name**

Attachment IV

Worst-Case Products

- ☐ Ciprofloxacin tablet 500 mg
- ☐ Diclofenac tablet 50 mg
- ☐ Ketotifen 1.0 mg tablets
- ☐ Sulfamethoxazole DS tablets

Calculation for Surface Swabs

$$\text{MAC} = \frac{\text{TD} \times \text{BS} \times \text{SF}}{\text{LDD}}$$

Calculation:

$$Y = X \times \text{surface area},$$

where Y is the active ingredient on the corresponding equipment part, X is the active ingredient recovered from 25 cm^2 by swab from the corresponding equipment part, and surface area is the area of the corresponding equipment parts A–I.

$$Z = Y1 + Y2 + Y3 + Y4 + Y5 + Y6 + Y7 + Y8 + Y9,$$

where Z is the total active ingredient recovered from the machine, $Y1$ is the active ingredient recovered from part S1, $Y2$ is the active ingredient recovered from part S2, $Y3$ is the active ingredient recovered from part S3, $Y4$ is the active ingredient recovered from part S4, $Y5$ is the active ingredient recovered from part S5, $Y6$ is the active ingredient recovered from part S6, $Y7$ is the active ingredient recovered from part S7, and $Y8$ is the active ingredient recovered from part S8.

Acceptance criteria:

$$Z \leq \text{MAC}.$$

Your Company's Logo **Your Company's Name**

Attachment V

Worst-Case Products

- ☐ Ciprofloxacin tablet 500 mg
- ☐ Diclofenac tablet 50 mg
- ☐ Ketotifen 1.0 mg tablets
- ☐ Sulfamethoxazole DS tablets

Training Record Verification (Production Staff)

The following staff found trained on cleaning of the equipment.

Using SOP No. ABC-004; Revision No.; Issued on; Date

Name: _____ ID No. _____ Sign. _____ Date _____

Name: _____ ID No. _____ Sign. _____ Date _____

Training Record Verification (Analyst)

The following analyst trained on STM No. _____

Name: _____ ID No. _____ Sign. _____ Date _____

Performed by: _____ Checked by: _____

Date: _____ Date: _____

Your Company's Logo **Your Company's Name**

Attachment VI

Worst-Case Products

- ☐ Ciprofloxacin tablet 500 mg
- ☐ Diclofenac tablet 50 mg
- ☐ Ketotifen 1.0 mg tablets
- ☐ Sulfamethoxazole DS tablets

Swab Analysis Results

Sampling Location	Visual Inspection	Detergent Determination (No Foam)	Carryover HPLC Result per 25 cm^2 (X)	Carryover 25 cm^2 × Surface Area Total Carryover $Y = X \times (A - I)$	Bio-Burden Test NMT 10 cfu/25 cm^2
S1					
S2					
S3					
S4					
S5					
S6					
S7					
S8					

Your Company's Logo **Your Company's Name**

Attachment VII

Swab Sampling Recovery (Challenge) Test

Name of Active Material	Concentration of Standard Solution	Type of Swab	Total Area of Swab	% Recovery of Active Ingredient	% Recovery as per Limit NLT (70%)	
					Y	N

CLV-20.4

Cleaning Validation Protocol for Powder Bins

Your Company's Logo

Your Company's Name

ABC Pharmaceutical Company	**CLEANING VALIDATION PROTOCOL** **Equipment Name**	
	Issued on **Date**	**Protocol Number** **CLVS-000**
	Location **Blending Area** **Room No.000**	

Equipment ..... **Powder Bin**

Model ..... **Model**

Manufacturer ..... **Company, Country**

Written by	**Signature & Date**
Validation Officer	_____
Reviewed by	**Signature & Date**
QA Manager	_____
	Signature & Date
QC Manager	_____
	Signature & Date
Production Manager	_____
Approved by	**Signature & Date**
Production Director	_____
Authorized by	**Signature & Date**
QA Director	_____

Your Company's Logo **Your Company's Name**

20.4.1 Objective

The objective is to demonstrate that the cleaning procedure will successfully and consistently reduce the level of residues to a predetermined level of acceptability, so as to prevent contaminants (products or cleaning process related) from adversely affecting the safety and quality of the next product manufactured.

20.4.2 Scope

This protocol will cover cleaning of the powder bins for the tablets products.

In the grouping matrix, products are divided into various groups based on their

a. Water solubility
b. Therapeutic dosage
c. Toxicity
d. Batch size (in kg)

From each group one worst-case product (Table 20.4.1) is considered for cleaning validation of bin-washing station (Figures 20.4.1 and 20.4.2).

20.4.3 Responsibility

The following personnel are responsible for the execution of this protocol:

Cleaning validation officer/production officer/QA inspector/machine operator.

For details, please refer to Attachment II.

TABLE 20.4.1

Worst-Case Products for Powder Bins

Products	Reason for Selecting as Worst Case
Ciprofloxacin 500 mg tablets	Six ingredients are insoluble in water
Ketotifen 1.0 mg tablets	Minimum therapeutic dose (1.0 mg)
Diclofenac 50 mg tablets	LD_{50}150 mg/kg oral rat
Sulfamethoxazole DS tablets	Largest batch size (825 kg)

Your Company's Logo **Your Company's Name**

FIGURE 20.4.1
Bin-washing station.

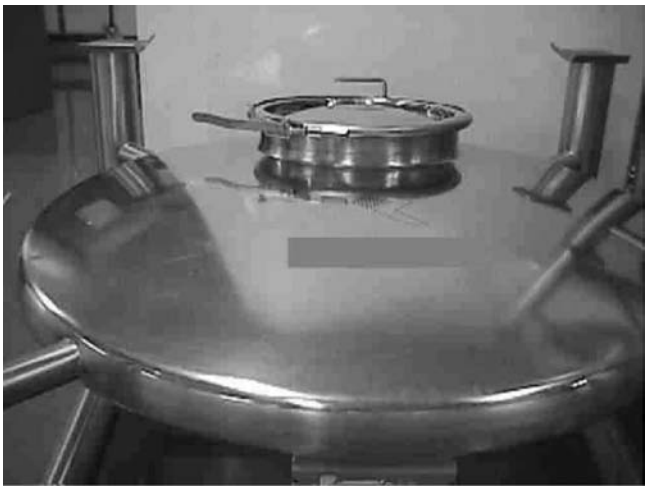


FIGURE 20.4.2
Bin.

Your Company's Logo

Your Company's Name

20.4.4 Description of the Cleaning Process

The powder bins are washed by bin-washing station, which is operated as per SOP No. ABC-002.

20.4.4.1 Difficult-to-Clean Parts

i. Top loading
ii. Inside corner portion
iii. Bottom unloading

20.4.5 Description of the Sampling Process

20.4.5.1 Sampling Technique

The surface swab sampling technique will be used to take samples from the powder bins.

20.4.5.2 Sampling Precautions

Before taking the sample, wear

i. Gloves
ii. Face mask

20.4.5.3 Procedure for Sampling

Samples for the internal surfaces will be taken by moistening the swab (ready-made sterile cotton swab) with a suitable solvent (DIW/alcohol–water–alcohol). Sample a 25-cm^2 area (refer to Figures 20.4.3 and 20.4.4) and place the swab in a test tube containing 10 mL of a solvent (suitable solvent). Swab samples from each part of the powder bins will be collected as per Table 20.4.2.

20.4.5.4 Handling of Samples

i. After collecting swab samples for MAC, they are kept in the refrigerator.
ii. Swab samples for the HPLC analysis were collected at the time of manufacturing; analysis to be completed within 24 h after collection.
iii. HPLC samples should be kept at room temperature for at least 2 h before testing.

Your Company's Logo

Your Company's Name

TABLE 20.4.2

Surface Swabs Sampling Description

Description	Sample Location	Sample ID	Reference
Powder bin	Bin neck right	S1	
	Bin neck right	S2	
	Bin neck right	S3	Figure 20.4.3
	Inside surface middle left	S4	
	Inside surface middle left	S5	
	Powder loading left	S6	
	Powder loading right	S7	Figure 20.4.4
	Powder loading center	S8	

20.4.6 Test Functions

a. *Visual inspection*: Inspection of powder bins will be performed visually at the end of the cleaning procedure.

b. *Maximum allowable carryover*: The test for MAC of the swab will be performed as per the HPLC method.

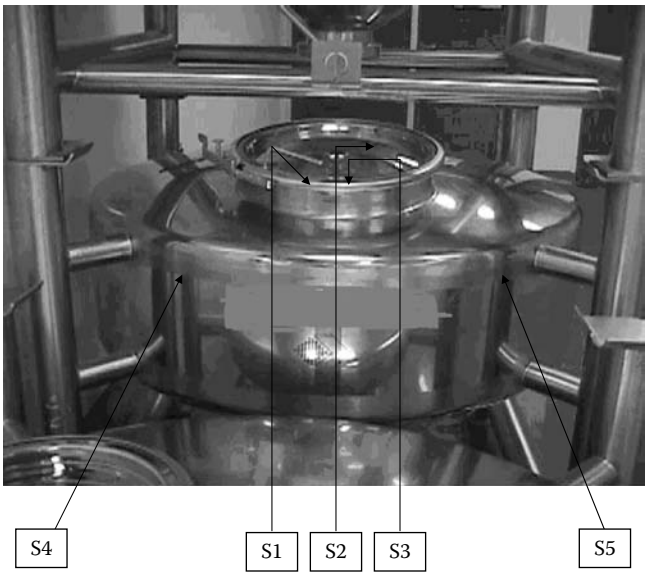


FIGURE 20.4.3
Bins loading inside sampling locations.

Your Company's Logo **Your Company's Name**

FIGURE 20.4.4
Bins offloading sampling locations.

Notes:

- Analysis will be carried out by pooling the 10 mL swabs extraction for specific analysis.
- The validated HPLC test method will be used for the determination of chemical residues.

c. *Bio-burden test*: The test for bio-burden will be performed as per STM No. MC-0001 by QC Microbiology section.

d. *Swab recovery challenge test*: The recovery challenge test of the swab sample will be performed as per PDA *Journal of Pharmaceutical Science and Technology*.

20.4.7 Verification of Documents

i. Verify the powder bin cleaning procedure
ii. Verify the powder bin cleaning logbook records
iii. Verify the cleaning operators and analyst training record (refer to Attachment V)

Your Company's Logo **Your Company's Name**

20.4.8 Documentation

i. All analysis results will be recorded in the analysis logbook.
ii. Printouts and chromatograms will be attached to the validation report and a copy of each will also be attached to the analytical logbook.
iii. A second analyst will verify all the data.
iv. A cleaning validation officer will check all training records.
v. The final report for cleaning validation will be prepared by the validation officer.

20.4.9 Acceptance Criteria

a. *Visual inspection*: The visible internal equipment surfaces and all critical and difficult-to-clean parts are optically free from residue and the color of the final rinse water is comparable to DIW.
b. *Maximum allowable carryover*: The active ingredient calculated (Z) is either equal to or less than the MAC. Based on the "worst-case" concept

$$Z \leq \text{MAC}$$

$$\text{MAC} = \frac{\text{TD} \times \text{BS} \times \text{SF}}{\text{LDD}},$$

where MAC is the maximum allowable carryover, TD is a single therapeutic dose, BS is the batch size of the next product to be manufactured in the same equipment, SF* is the safety factor (0.001), and LDD is the largest daily dose of the next product to be manufactured in the same equipment.

The calculated value will be the maximum amount of active ingredient of worst-case product that is allowed to be carried over to the next batch.

Calculation:

$$Y = X \times \text{surface area},$$

where Y is the active ingredient on the corresponding equipment part, X is the active ingredient recovered from 25 cm^2 by swab from the corresponding equipment part, and surface area is the area of the corresponding equipment parts A–H.

$$Z = Y1 + Y2 + Y3 + Y4 + Y5 + Y6 + Y7 + Y8$$

* 1/100 to 1/1000 of a normal daily dose for oral products (PDA Guideline).

where Z is the total active ingredient recovered from the machine, $Y1$ is the active ingredient recovered from part S1, $Y2$ is the active ingredient recovered from part S2, $Y3$ is the active ingredient recovered from part S3, $Y4$ is the active ingredient recovered from part S4, $Y5$ is the active ingredient recovered from part S5, $Y6$ is the active ingredient recovered from part S6, $Y7$ is the active ingredient recovered from part S7, and $Y8$ is the active ingredient recovered from part S8.

Acceptance criteria:

$$Z \leq \text{MAC}.$$

c. *Bio-burden*: The bio-Burden should not be more than 33 cfu/25 cm^2 for the swabs.

d. *Swab recovery challenge test*: The swab recovery challenge test should be NLT 70% of the known concentration of standard spiked.

20.4.10 List of Attachments

Attachment I	Description of equipment and product
Attachment II	Cleaning/testing responsibilities
Attachment III	Sampling and testing plan.
Attachment IV	Calculations for surface swabs.
Attachment V	Training record verification
Attachment VI	Swabs analysis results
Attachment VII	Swab sampling recovery challenge test results

Your Company's Logo **Your Company's Name**

Attachment I

Description of Equipment and Product

Equipment Name: _____

Serial No.: _____

Capacity: _____

Location: _____

Room No.: _____

Product Name: _____

Batch No. of the Product: _____

Next Product to Be Manufactured in the Same Equipment: _____

Manufacturing Date: _____

Active Ingredient: _____

Therapeutic Group: _____

Cleaning Date: _____

Cleaning SOP No.: _____ Revision No.: _____

Sampling Technique: _____

Cleaning Sample Analysis Date/Time: _____ Result: _____

Test Method Reference: _____ Reference Analytical Logbook: _____

Limit of Detection: _____

Safety Factor: _____

Worst-Case Products

- ☐ Ciprofloxacin tablet 500 mg
- ☐ Diclofenac tablet 50 mg
- ☐ Ketotifen 1.0 mg tablets
- ☐ Sulfamethoxazole DS tablets

Your Company's Logo **Your Company's Name**

Attachment II

Cleaning/Testing Responsibilities

Cleaning/Testing	Done by	Recorded on	Checked by
Equipment cleaning	Machine operator	Equipment usage/ cleaning logbook	Production supervisor
Visual inspection	Validation officer	Analytical logbook	—
Swab sample	Machine operator/ validation officer	Sampling sheet	—
MAC	Validation officer/ QC analyst	Analytical logbook	QC officer
Bio-burden	Microbiologist	Analytical logbook	Manager QC, microbiology
Swab recovery challenge test	Analyst	Analytical logbook	Senior analyst

Your Company's Logo **Your Company's Name**

Attachment III

Worst-Case Products

- ☐ Ciprofloxacin tablet 500 mg
- ☐ Diclofenac tablet 50 mg
- ☐ Ketotifen 1.0 mg tablets
- ☐ Sulfamethoxazole DS tablets

Sampling and Testing Plan

S. No.	Visual Inspection	Identification Labeling	Sample Area (cm^2)	Surface Area in Contact with Product (cm^2)	MAC	Less Than or Equal to Limit of Detection	Testing Method	Bio-Burden NMT 33 cfu/25 cm^2	Testing Method
1.		S1	25	27,240					
2.		S2	25	27,240					
3.		S3	25	27,240					
4.		S4	25	27,240					
5.		S5	25	27,240					
6.		S6	25	27,240					
7.		S7	25	27,240					
8.		S8	25	27,240					

Your Company's Logo **Your Company's Name**

Attachment IV

Calculation for Surface Swabs

$$\text{MAC} = \frac{\text{TD} \times \text{BS} \times \text{SF}}{\text{LDD}}$$

Calculation:

$$Y = X \times \text{surface area},$$

where Y is the active ingredient on the corresponding equipment part, I is the active ingredient recovered from 25 cm^2 by swab from the corresponding equipment part, and surface area is the area of the corresponding equipment parts A–H.

$$Z = Y1 + Y2 + Y3 + Y4 + Y5 + Y6 + Y7 + Y8,$$

where Z is the total active ingredient recovered from machine, $Y1$ is the active ingredient recovered from part S1, $Y2$ is the active ingredient recovered from part S2, $Y3$ is the active ingredient recovered from part S3, $Y4$ is the active ingredient recovered from part S4, $Y5$ is the active ingredient recovered from part S5, $Y6$ is the active ingredient recovered from part S6, $Y7$ is the active ingredient recovered from part S7, $Y8$ is the active ingredient recovered from part S8.

Acceptance criteria:

$$Z \leq \text{MAC}.$$

Your Company's Logo **Your Company's Name**

Attachment V

Training Record Verification (Production Staff)

The following staff found trained on cleaning of the equipment.

Using SOP No. ABC-004; Revision No. Issued on; Date

Training Record Verification (Analyst)

The following analyst trained on STM No. _____

Name: _____ ID No. _____ Sign. _____ Date _____

Name: _____ ID No. _____ Sign. _____ Date _____

Name: _____ ID No. _____ Sign. _____ Date _____

Performed by: _____ Checked by: _____

Date: _____ Date: _____

Your Company's Logo **Your Company's Name**

Attachment VI

Worst-Case Products

- ☐ Ciprofloxacin tablet 500 mg
- ☐ Diclofenac tablet 50 mg
- ☐ Ketotifen 1.0 mg tablets
- ☐ Sulfamethoxazole DS tablets

Swab Analysis Results

Sampling Location	Visual Inspection	Bio-Burden Test NMT 33 cfu/swab	Carryover HPLC Result per 25 cm^2 (X)	Carryover 25 cm^2 × Surface Area Total Carryover $Y = X \times (A–H)$
S1				
S2				
S3				
S4				
S5				
S6				
S7				
S8				

Your Company's Logo **Your Company's Name**

Attachment VII

Swab Sampling Recovery (Challenge) Test

Name of Active Material	Concentration of Standard Solution	Type of Swab	Total Area of Swab	% Recovery of Active Ingredient	% Recovery as per Limit NLT 70%	
					Y	N

CLV-20.5

Cleaning Validation Protocol for Tablet Press

Your Company's Logo

Your Company's Name

ABC Pharmaceutical Company	**CLEANING VALIDATION PROTOCOL** **Equipment Name**	
	Issued on **Date**	**Protocol Number** **CLVS-000**
	Location **ABC Pharmaceutical Company** **(Compression Area)** **Room No. 000**	

Equipment ..... **Tablet Compression**

Model ..... **Model**

Manufacturer ..... **Company, Country**

Written by	**Signature & Date**
QA Officer	_____
Reviewed by	**Signature & Date**
QA Manager	_____
	Signature & Date
QC Manager	_____
	Signature & Date
Production Manager	_____
Approved by	**Signature & Date**
Production Director	_____
Authorized by	**Signature & Date**
QA Director	_____

Your Company's Logo

Your Company's Name

20.5.1 Cleaning Validation Protocol for Tablet Press Type A

20.5.1.1 Objective

The objective is to demonstrate that the cleaning procedure No. ABC-001 will successfully and consistently reduce the level of residues to a predetermined level of acceptability, so as to prevent contaminantion (product or cleaning process related) from adversely affecting the safety and quality of the next product manufactured.

20.5.1.2 Scope

This protocol will the cover cleaning process of the tablet compression machine located in room 000.

As per the MVP grouping matrix, products are divided into various groups based on their

a. Water solubility
b. Therapeutic dosage
c. Toxicity
d. Batch size (in kg)

From each group, one worst-case product is considered for cleaning validation (Table 20.5.1.1).

20.5.1.3 Responsibility

The following personnel are responsible for the execution of this protocol:

QA officer/production officer/QA inspector/QC chemist/analyst/machine operator.

For details, please refer to Attachment II.

20.5.1.4 Description of the Cleaning Process

The tablet compression machine is to be cleaned manually as per SOP No. ABC-001.

TABLE 20.5.1.1

Worst-Case Products of Compression Machine

Products	Reason for Selecting as Worst Case
Ciprofloxacin 500 mg tablets	Six ingredients are insoluble in water
Ketotifen 1.0 mg tablets	Minimum therapeutic dose (1.0 mg)
Diclofenac 50 mg tablets	LD_{50}150 mg/kg oral rat
Sulfamethoxazole DS tablets	Largest batch size (825 kg)

Your Company's Logo **Your Company's Name**

4.1 Label the machine "UNDER CLEANING"
4.2 Run the machine and the Fill-O-Matic for 1 min to clear out the powder from the hopper and Fill-O-Matic
4.3 Open the machine door
4.4 Remove the excess powder inside the machine by a vacuum cleaner
4.5 Remove the hopper
4.6 Remove the Fill-O-Matic
4.7 Remove the scraper
4.8 Remove the tablet-discharge chute and panels
4.9 Remove the tablet deduster and hoses
4.10 Dismantle the fill cam
4.11 Take out the upper and lower punches with the help of the mobile control box and keep them in a suitable tray, or take out die plate subassembly as per SOP No. ABC-003 if required
4.12 Unscrew the die fixing screws and lift out the dies and keep them in a tray
4.13 Clean the inside of the machine thoroughly with white sprite by means of brushes
4.14 Blow the die plate with compressed air
4.15 Clean the upper and lower punches of dies and fill cam with white sprite by means of brushes, apply oil, and keep them in a plastic cover, and arrange them in a plastic tray
4.16 Wipe the die plate, die holes, upper and lower punches holes, and the inside of the machine with a clean towel
4.17 Clean the inside glass doors with a clean towel wetted with white sprite
4.18 Close the machine door
4.19 Clean the upper side of the machine and the outside of the machine with a clean wet towel
4.20 Clean the control panel with a clean wet towel
4.21 Shake the dust extraction unit and collect the powder from it in a polythene bag and label it as a pharmaceutical waste
4.22 Clean the powder collector tray of the dust extraction unit with water and dry it with compressed air
4.23 Clean the outside and the upper side of the dust extraction unit with a clean wet towel
4.24 Collect the broken tablets from the check master and label them as a pharmaceutical waste
4.25 Clean the check master from inside and outside and the glass collector with a clean wet towel

Your Company's Logo **Your Company's Name**

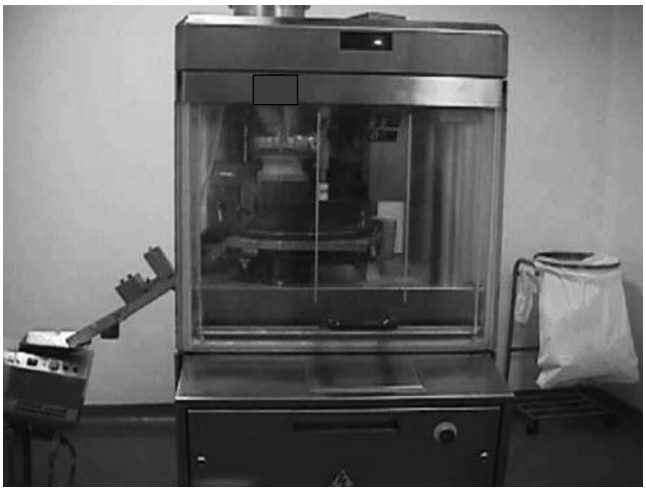


FIGURE 20.5.1.1
Compression machine type A.

4.26 Clean the hopper, Fill-O-Matic, tablet-discharge chute, hoses and uphill tablet deduster parts with water and dry them with compressed air
4.27 Clean the outside parts of the tablet deduster with a clean wet towel
4.28 Assemble the machine for the required product as described in the SOP
4.29 Label the machine "CLEAN"
4.30 Make entries in the cleaning, maintenance and production usage logbook as per SOP

20.5.1.5 Difficult-to-Clean Parts

i. Powder hose
ii. Disc below punches
iii. Powder hopper
iv. Rubber mold
v. Fill-O-Matic

20.5.1.6 Description of the Sampling Process

20.5.1.6.1 Sampling Technique

The surface swab sampling technique will be used to take samples from the tablet compression machine.

Surface swabs (swabs with diluents including a suitable neutralizing agent).

Your Company's Logo

Your Company's Name

20.5.1.6.2 Sampling Precautions

Before taking samples, wear

i. Gloves
ii. Face mask

20.5.1.6.3 Surface Swabs

20.5.1.6.3.1 Procedure for Sampling

Samples for the internal surfaces will be taken by moistening the swab (ready-made sterile cotton swab) with a suitable solvent (DIW/alcohol–water–alcohol). Sample a 25-cm^2 area (see Figures 20.5.1.2 through 20.5.1.7) and place the swab in a test tube containing 10 mL of solvent (suitable solvent). Swab samples from each part of the compression machine will be collected as per Table 20.5.1.2.

20.5.1.7 Test Functions

a. *Visual inspection:* Inspection of the tablet compression machine will be performed visually.
b. *Maximum allowable carryover:* The test for MAC of the final swab will be performed as per the HPLC method suitable for each product residue.

Notes:

- Analysis will be carried out by pooling the 10 mL swabs extraction for specific analysis
- The validated HPLC test method will be used for the determination of chemical residues

TABLE 20.5.1.2

Surface Swabs Sampling Description

Description	Sample Location	Sample ID	Reference
Tablet compression machine	Body surface left	S1	Figure 20.5.1.2
	Body surface right	S2	
	Fill-O-Matic	S3	
	Powder hopper joints	S4	Figure 20.5.1.3
	Powder hopper	S5	
	Tablet discharge 1	S6	Figure 20.5.1.4
	Tablet discharge 2	S7	Figure 20.5.1.5
	Tablet discharge 3	S8	
	Tablet rotator disc	S9	Figure 20.5.1.6
	Tablet discharge 4	S10	Figure 20.5.1.7

Your Company's Logo **Your Company's Name**

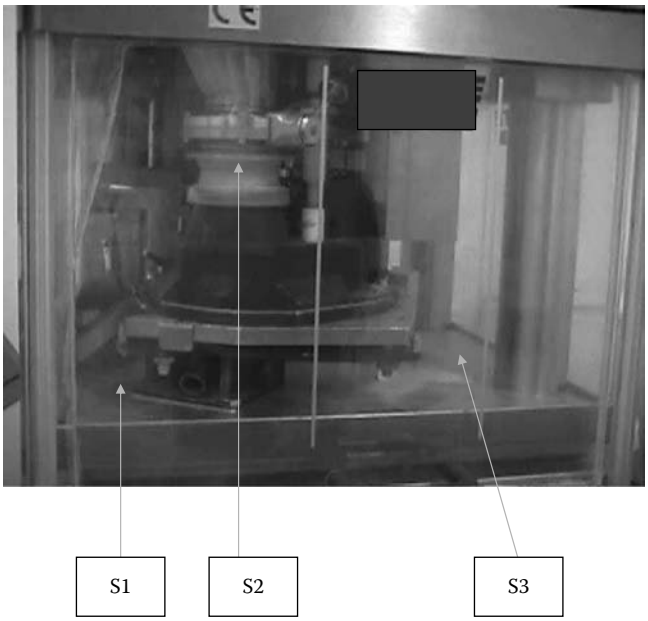


FIGURE 20.5.1.2
Compression machine inside surface and turret sampling locations.

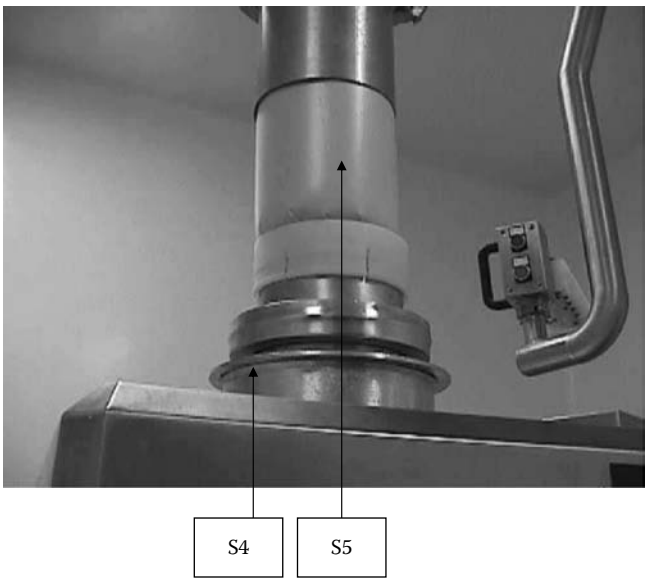


FIGURE 20.5.1.3
Powder chute sampling location.

Your Company's Logo **Your Company's Name**

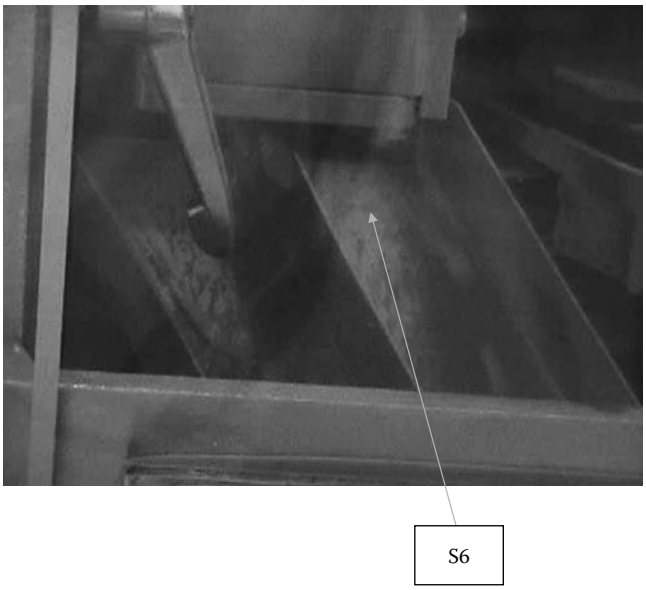


FIGURE 20.5.1.4
Tablets discharge chute sampling location.

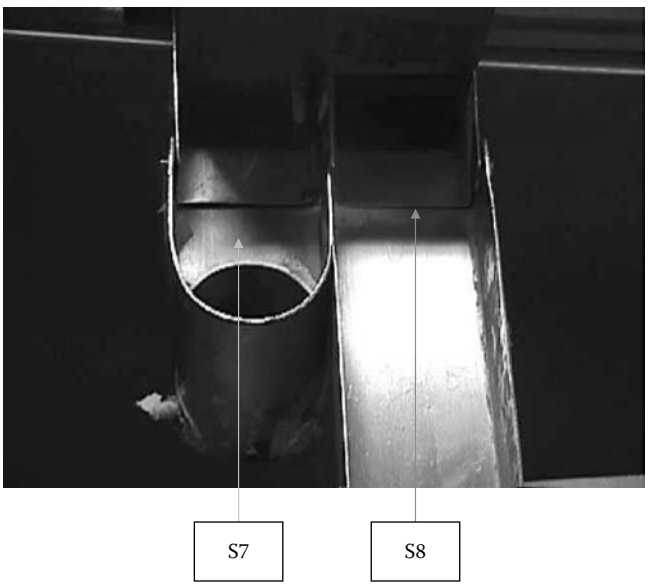


FIGURE 20.5.1.5
Opening of discharge chute.

Your Company's Logo **Your Company's Name**

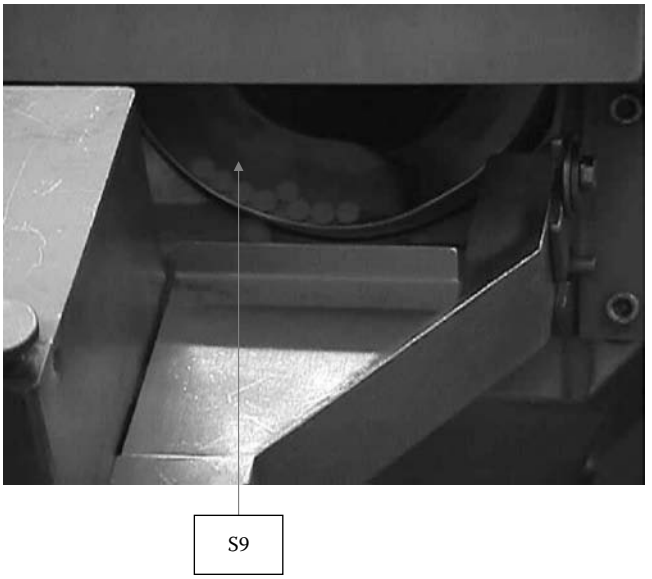


FIGURE 20.5.1.6
Discharge chute.

FIGURE 20.5.1.7
Discharge chute.

Your Company's Logo **Your Company's Name**

c. *Bio-burden test:* The test for Bio-burden will be performed as per STM No. MC-001, by the Microbiology section.
d. *Swab recovery challenge test:* The recovery challenge test of the swab sample will be performed as per PDA General Guideline.
e. *Detergent detection:* The test for the detergent detection will be performed as per procedure No. ABC-004.

20.5.1.8 Verification of Documents

i. Verify the tablet compression machine cleaning procedure.
ii. Verify the tablet compression machine cleaning logbook records.
iii. Verify the cleaning operators and the analyst training record (refer to Attachment V).

20.5.1.9 Documentation

i. All analysis results will be recorded in the analysis logbook.
ii. Printouts and chromatograms will be attached to the validation report and a copy of that is also attached to the analytical logbook.
iii. A second analyst will verify all analyses and data.
iv. A QA officer will check all training records.
v. The final report for cleaning validation will be prepared by a QA officer.

20.5.1.10 Acceptance Criteria

a. *Visual inspection:* The visible internal equipment surfaces and all critical and difficult-to-clean parts are optically free from residue and the color of the final rinse water is comparable to DIW.
b. *Maximum allowable carryover:* The active ingredient calculated (Z) is either equal to or less than the MAC. Based on the "worst-case" concept

$$Z \leq \text{MAC},$$

$$\text{MAC} = \frac{\text{TD} \times \text{BS} \times \text{SF}}{\text{LDD}},$$

where MAC is the maximum allowable carryover, TD is a single therapeutic dose, BS is the batch size of the next product to be manufactured in the same equipment, SF* is the safety factor (0.001), and LDD is the largest daily dose of the next product to be manufactured in the same equipment.

* 1/100 to 1/1000 of a normal daily dose for oral products (PDA Guideline).

Your Company's Logo **Your Company's Name**

The calculated value will be the maximum amount of active ingredient of product that is allowed to be carried over to the next batch.

Calculation:

$$Y = X \times \text{surface area},$$

where Y is the active ingredient on the corresponding equipment part, X is the active ingredient recovered from 25 cm^2 by swab from the corresponding equipment part, and surface area is the area of the corresponding equipment parts A–J.

$$Z = Y1 + Y2 + Y3 + Y4 + Y5 + Y6 + Y7 + Y8 + Y9 + Y10,$$

where Z is the total active ingredient recovered from the machine, $Y1$ is the active ingredient recovered from part S1, $Y2$ is the active ingredient recovered from part S2, $Y3$ is the active ingredient recovered from part S3, $Y4$ is the active ingredient recovered from part S4, $Y5$ is the active ingredient recovered from part S5, $Y6$ is the active ingredient recovered from part S6, $Y7$ is the active ingredient recovered from part S7, $Y8$ is the active ingredient recovered from part S8, $Y9$ is the active ingredient recovered from part S9, and $Y10$ is the active ingredient recovered from part S10.

Acceptance criteria:

$$Z \leq \text{MAC}.$$

c. *Bio-burden:* The bio-burden should not be more than 33 cfu/25 cm^2 for the swabs.
d. *Swab recovery challenge test:* The swab recovery challenge test should be NLT 70% of the known concentration of standard spiked.
e. *Detergent detection:* No foam was detected on top of the sample after testing.

20.5.1.11 List of Attachments

Attachment I	Description of equipment and product
Attachment II	Cleaning/testing responsibilities
Attachment III	Sampling and testing plan
Attachment IV	Calculations for surface swabs
Attachment V	Training record verification
Attachment VI	Swab analysis results
Attachment VII	Swab sampling recovery challenge test results

Your Company's Logo **Your Company's Name**

Attachment I

Description of Equipment and Product

Equipment Name: _____

Serial No.: _____

Capacity: _____

Validated on: _____

Room No.: _____

Product Name: _____

Product Batch No.: _____

Next Product to Be Manufactured in the Same Equipment: _____

Manufacturing Date: _____

Active Ingredient: _____

Therapeutic Group: _____

Cleaning Date: _____

Cleaning SOP No.: _____ Revision No.: _____

Sampling Technique: _____

Cleaning Sample Analysis Date/Time: _____ Result: _____

Test Method Reference: _____ Reference Analytical Logbook: _____

Limit of Detection: _____

Safety Factor: _____

Your Company's Logo **Your Company's Name**

Attachment II

Cleaning/Testing Responsibilities

Cleaning/Testing	Done by	Recorded on	Checked by
Equipment cleaning	Machine operator	Equipment usage/ cleaning logbook	Production supervisor
Visual inspection	Validation officer	Analytical logbook	—
Swab sample	Machine operator/ validation officer	Sampling sheet	QA officer
pH/detergent determination	Validation officer/QC analyst	Analytical logbook	QA/QC officer
MAC	Validation officer/QC analyst	Analytical logbook	QC officer
Bio-burden	Microbiologist	Analytical logbook	QC microbiology manager
Swab recovery challenge test	QC analyst	Analytical logbook	QC senior analyst

Your Company's Logo **Your Company's Name**

Attachment III

Sampling and Testing Plan

S. No.	Visual Inspection	Identification Labeling	Sample Area (cm^2)	Surface Area (cm^2)	MAC	Less Than or Equal to Limit of Detection	Bio-Burden NMT 33 cfu/ swab	Testing Method
1.		S1	25	22,795				STM-MC-001
2.		S2	25	2005				
3.		S3	25	22,795				
4.		S4	25	7295				
5.		S5	25	8105				
6.		S6	25	3845				
7.		S7	25	605				
8.		S8	25	1205				
9.		S9	25	6445				
10.		S10	25	2585				

Your Company's Logo **Your Company's Name**

Attachment IV

Calculation for Surface Swabs

Formula:

$$\text{MAC} = \frac{\text{TD} \times \text{BS} \times \text{SF}}{\text{LDD}}.$$

Calculation:

$$Y1 = X \times \text{A},$$

where $Y1$ is the active ingredient on the equipment part A, X is the active ingredient recovered from 25 cm^2 by swab from part A, and A is the surface area of equipment part A.

$$Z = Y1 + Y2 + Y3 + Y4 + Y5 + Y6 + Y7 + Y8 + Y9 + Y10,$$

where Z is the total active ingredient recovered from the machine, $Y1$ is the active ingredient recovered from part S1, $Y2$ is the active ingredient recovered from part S2, $Y3$ is the active ingredient recovered from part S3, $Y4$ is the active ingredient recovered from part S4, $Y5$ is the active ingredient recovered from part S5, $Y6$ is the active ingredient recovered from part S6, $Y7$ is the active ingredient recovered from part S7, $Y8$ is the active ingredient recovered from part S8, $Y9$ is the active ingredient recovered from part S9, and $Y10$ is the active ingredient recovered from part S10.

Acceptance criteria:

$$Z \leq \text{MAC}$$

Your Company's Logo **Your Company's Name**

Attachment V

Training Record Verification (Production Staff)

The following staff found trained on cleaning of the equipment.

Using SOP No. ABC-005; Revision No. 0; Issued on; Date

Name: _____ ID No. _____ Sign. _____ Date _____

Name: _____ ID No. _____ Sign. _____ Date _____

Training Record Verification (Analyst)

The following analyst trained on STM No. _____

Name: _____ ID No. _____ Sign. _____ Date _____

Performed by: _____ Checked by: _____

Date: _____ Date: _____

Your Company's Logo **Your Company's Name**

Attachment VI

Swab Analysis Results

Sampling Location	Visual Inspection	Detergent Detection (No Foam)	Bio-Burden Test NMT 33 cfu/mL	Carryover HPLC Result per 25 cm^2 (X)	Carryover 25 cm^2 × Surface Area Total Carryover $Y = X \times$ Surface Area
S1					
S2					
S3					
S4					
S5					
S6					
S7					
S8					
S9					
S10					

Your Company's Logo **Your Company's Name**

Attachment VII

Swab Sampling Recovery (Challenge) Test

Name of Active Material	Concentration of Standard Solution	Type of Swab	Total Area of Swab	% Recovery of Active Ingredient	% Recovery as per NLT (70%)	
					Y	N

Your Company's Logo **Your Company's Name**

20.5.2 Cleaning Validation Protocol for Tablet Press Type B (Figure 20.5.2.1)

Since the equipment is not identical, the sampling points and plan will be changed as per the design and size of the equipment.

In the following pages, the sampling plan and pictures of the type B and similarly type C tablet press are given with the selected sampling sites. See Figures 20.5.2.2 through 20.5.2.8 for sampling locations of tablet compression machine type B.

FIGURE 20.5.2.1
Front view: Tablet compression machine type B.

Your Company's Logo **Your Company's Name**

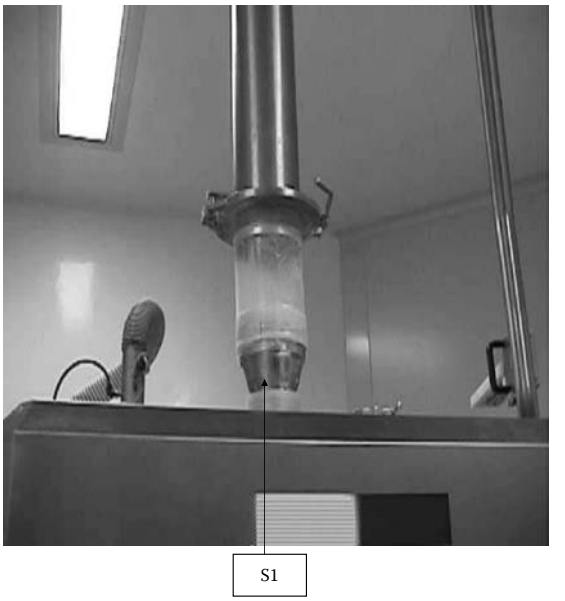


FIGURE 20.5.2.2
Powder-loading hose.

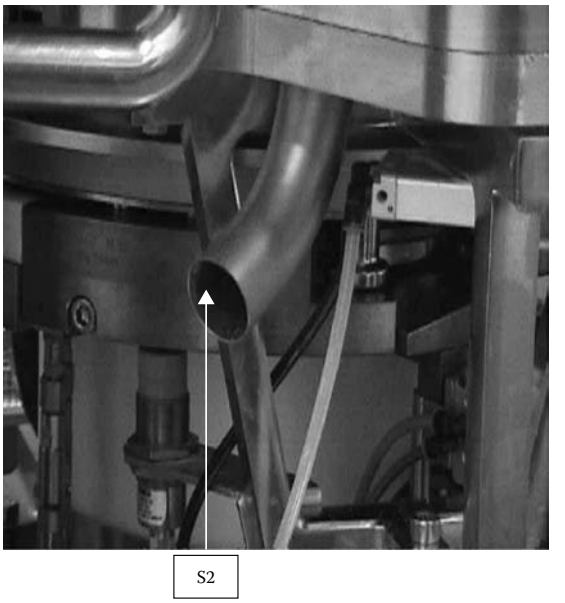


FIGURE 20.5.2.3
Opening of tablet-discharge chute.

Your Company's Logo **Your Company's Name**

FIGURE 20.5.2.4
Discharge chute.

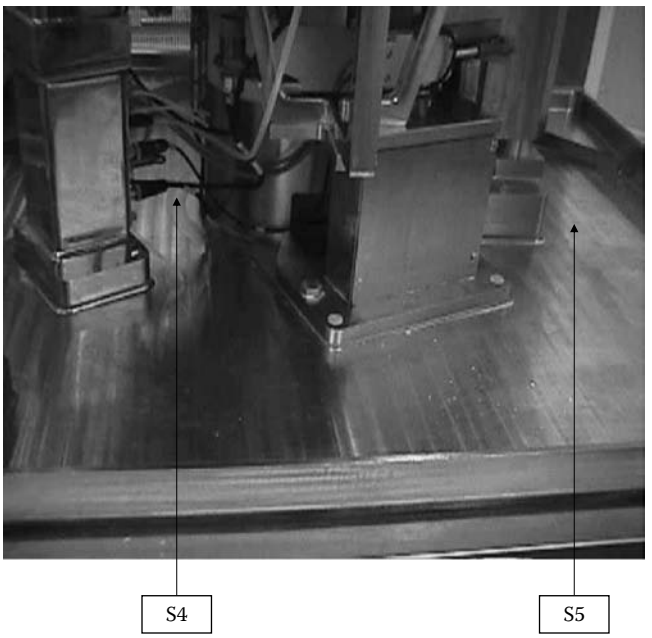


FIGURE 20.5.2.5
Body surface.

Your Company's Logo **Your Company's Name**

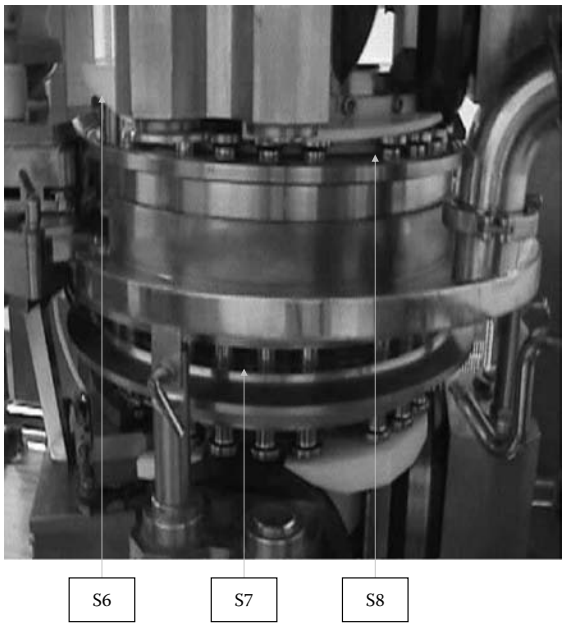


FIGURE 20.5.2.6
Disc below punches.

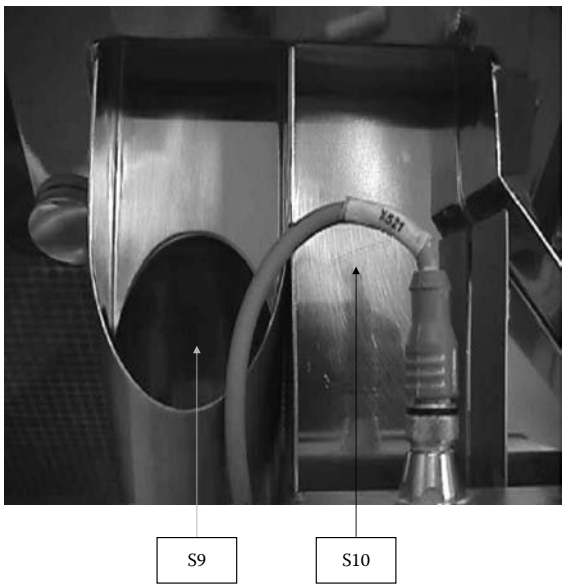


FIGURE 20.5.2.7
Rejection chute and tray.

Your Company's Logo **Your Company's Name**

FIGURE 20.5.2.8
Tablets channel.

Your Company's Logo **Your Company's Name**

Attachment III

Sampling and Testing Plan

S. No.	Visual Inspection	Identification Labeling	Sample Area (cm^2)	Surface Area (cm^2)	MAC	Less Than or Equal to Limit of Detection	Bio-Burden NMT 33 cfu/25 cm^2	Testing Method
1.		S1	25	810				STM-MC-001
2.		S2	25	60				
3.		S3	25	32				
4.		S4	25	8320				
5.		S5	25	8320				
6.		S6	25	40				
7.		S7	25	5000				
8.		S8	25	5000				
9.		S9	25	120				
10.		S10	25	60				
11.		S11	25	56				
12.		S12	25	56				
13.		S13	25	56				

Your Company's Logo **Your Company's Name**

Attachment IV

Calculation for Surface Swabs

$$\text{MAC} = \frac{\text{TD} \times \text{BS} \times \text{SF}}{\text{LDD}}.$$

Calculation:

$$Y1 = X \times \text{surface area},$$

where Y is the active ingredient on the Corresponding equipment part, X is the active ingredient recovered from 25 cm^2 by swab from the corresponding equipment part, and surface area is the area of the corresponding equipment part A–M.

$$Z = Y1 + Y2 + Y3 + Y4 + Y5 + Y6 + Y7 + Y8 + Y9 + Y10 + Y11 + Y12 + Y13,$$

where Z is the total active ingredient recovered from the machine, $Y1$ is the active ingredient recovered from part S1, $Y2$ is the active ingredient recovered from part S2, $Y3$ is the active ingredient recovered from part S3, $Y4$ is the active ingredient recovered from part S4, $Y5$ is the active ingredient recovered from part S5, $Y6$ is the active ingredient recovered from part S6, $Y7$ is the active ingredient recovered from part S7, $Y8$ is the active ingredient recovered from part S8, $Y9$ is the active ingredient recovered from part S9, and $Y10$ is the active ingredient recovered from part S10, $Y11$ is the active ingredient recovered from part S11, and $Y12$ is the active ingredient recovered from part S12, $Y13$ is the active ingredient recovered from part S13.

Acceptance criteria:

$$Z \leq \text{MAC}.$$

Your Company's Logo **Your Company's Name**

Attachment V

Training Record Verification (Production Staff)

The following staff found trained on cleaning of the equipment.

Using SOP No. ABC-006; Revision No.; Issued on; Date

And SOP No. ABC-007; Revision No.; Issued on; Date

Name: _____ ID No. _____ Sign. _____ Date _____

Name: _____ ID No. _____ Sign. _____ Date _____

Training Record Verification (Analyst)

The following analyst trained on STM No. _____

Name: _____ ID No. _____ Sign. _____ Date _____

Performed by: _____ Checked by: _____

Date: _____ Date: _____

Your Company's Logo **Your Company's Name**

Attachment VI

Swab Analysis Results

Sampling Location	Visual Inspection	Detergent Detection (No Foam)	Bio-Burden Test NMT 33 cfu/mL	Carryover HPLC Result per 25 cm^2 (X)	Carryover 25 cm^2 × Surface Area Total Carryover $Y = X \times$ Surface Area
S1					
S2					
S3					
S4					
S5					
S6					
S7					
S8					
S9					
S10					
S11					
S12					
S13					

Your Company's Logo **Your Company's Name**

Attachment VII

Swab Sampling Recovery (Challenge) Test

Name of Active Material	Concentration of Standard Solution	Type of Swab	Total Area of Swab	% Recovery of Active Ingredient	% Recovery as per NLT (70%)	
					Y	N

Your Company's Logo **Your Company's Name**

20.5.3 Cleaning Validation Protocol for Tablet Press Type C (Figure 20.5.3.1)

For swab sampling location see Figures 20.5.3.2 through 20.5.3.8.
Calculation:

$$Y = X \times \text{surface area},$$

where Y is the active ingredient on the corresponding equipment part, X is the active ingredient recovered from 25 cm^2 by swab from the corresponding equipment part, And surface area is the area of the corresponding equipment parts A–M.

$$Z = Y1 + Y2 + Y3 + Y4 + Y5 + Y6 + Y7 + Y8 + Y9 + Y10 + Y11 + Y12,$$

where Z is the total active ingredient recovered from the machine, $Y1$ is the active ingredient recovered from part S1, $Y2$ is the active ingredient recovered from part S2, $Y3$ is the active ingredient recovered from part S3, $Y4$ is the active ingredient recovered from part S4, $Y5$ is the active ingredient recovered from part S5, $Y6$ is the active ingredient recovered from part S6, $Y7$ is the active ingredient recovered from part 7, $Y8$ is the active ingredient recovered from part 8, $Y9$ is the active ingredient recovered from part 9, $Y10$ is the active ingredient recovered from part 10, $Y11$ is the active ingredient recovered from part 11, and $Y12$ is the active ingredient recovered from part 12.
Acceptance criteria:

$$Z \leq \text{MAC}.$$

a. *Bio-burden:* The bio-Burden should not be more than 10 cfu/100 mL for the rinses and not more than 33 cfu/25 cm^2 for the swabs.
b. *Swab recovery challenge test:* The swab recovery challenge test should be 70% of the known concentration of standard spiked.

20.5.3.1 List of Attachments

Attachment I	Description of equipment and product
Attachment II	Cleaning/testing responsibilities
Attachment III	Sampling and testing plan
Attachment IV	Calculations for surface swabs
Attachment V	Training record verification
Attachment VI	Swabs analysis results
Attachment VII	Swab sampling recovery challenge test results

Your Company's Logo **Your Company's Name**

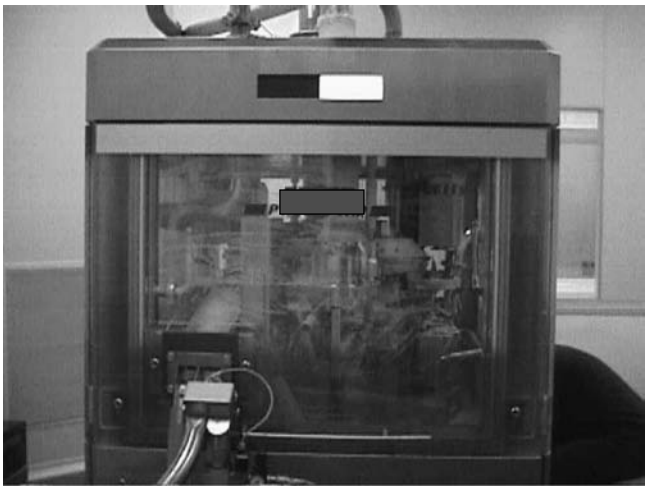


FIGURE 20.5.3.1
Tablet compression machine type C.

FIGURE 20.5.3.2
Tablet-discharge chute.

Your Company's Logo **Your Company's Name**

FIGURE 20.5.3.3
Tablet-discharge chute.

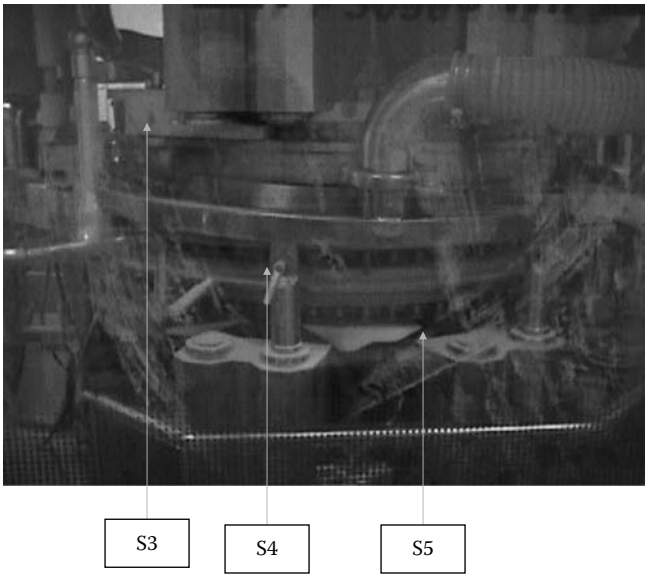


FIGURE 20.5.3.4
Die, punches, disc, and Fill-O-Matic.

Your Company's Logo **Your Company's Name**

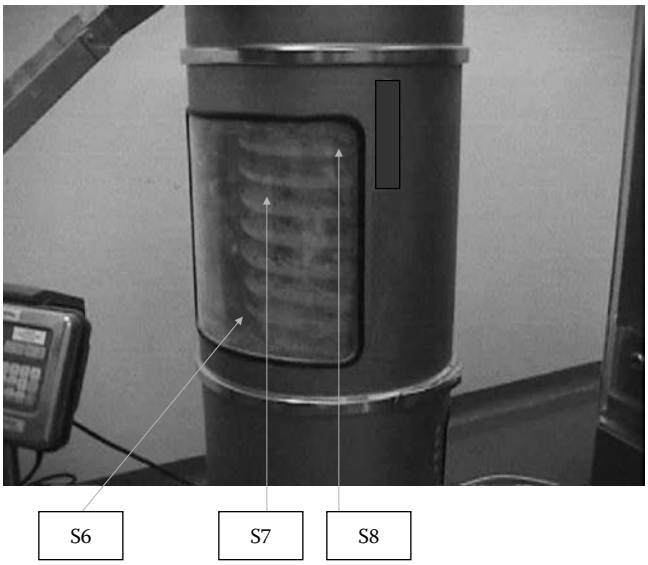


FIGURE 20.5.3.5
Tablets channel.

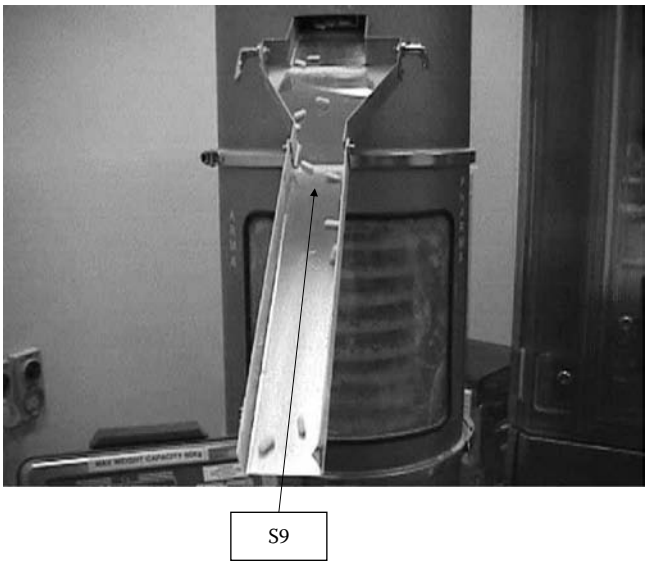


FIGURE 20.5.3.6
Tablet-discharge tray.

Your Company's Logo **Your Company's Name**

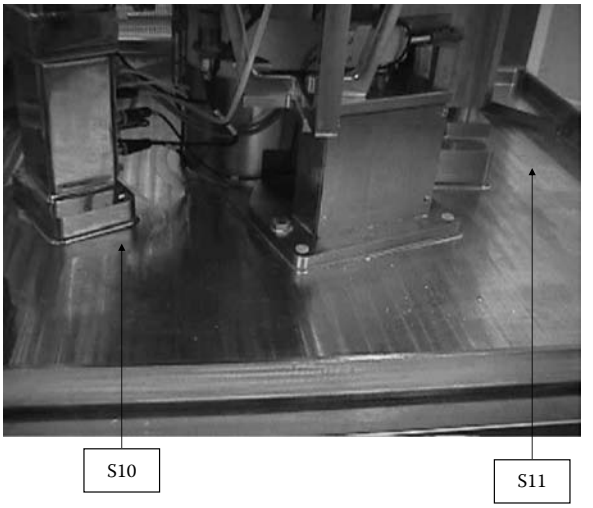


FIGURE 20.5.3.7
Body surface.

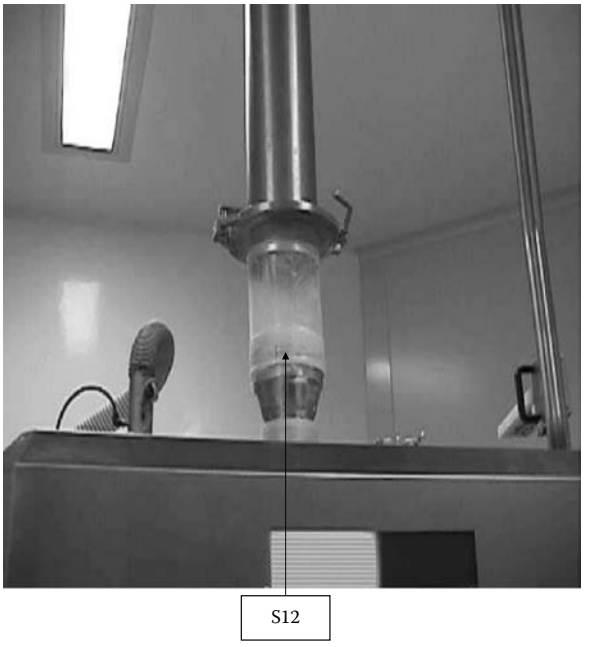


FIGURE 20.5.3.8
Powder-loading hose.

Your Company's Logo **Your Company's Name**

Attachment I

Description of Equipment and Product

Equipment Name: _____

Serial No.: _____

Capacity: _____

Location: _____

Room No.: _____

Name of the Product: _____

Batch No. of the Product: _____

Next Product to Be Manufactured in the Same Equipment: _____

Manufacturing Date: _____

Active Ingredient: _____

Therapeutic Group: _____

Cleaning Date: _____

Cleaning SOP No.: _____ Revision No.: _____

Sampling Technique: _____

Cleaning Sample Analysis Date/Time: _____ Assay Result: _____

Test Method Reference: _____ Reference Analytical Logbook: _____

Limit of Detection: _____

Safety Factor: _____

Your Company's Logo **Your Company's Name**

Attachment II

Cleaning/Testing Responsibilities

Cleaning/Testing	Done by	Recorded on	Checked by
Equipment cleaning	Machine operator	Equipment usage/ cleaning logbook	Production supervisor
Visual inspection	Validation officer	Analytical logbook	—
Swab sample	Machine operator/ validation officer	Sampling sheet	—
MAC	Validation officer/QC analyst	Analytical logbook	QC analyst
Bio-burden	Microbiologist	Analytical logbook	QC manager, microbiology
Swab recovery challenge test	Analyst	Analytical logbook	Senior analyst

Your Company's Logo **Your Company's Name**

Attachment III

Sampling and Testing Plan

S. No.	Visual Inspection	Identification Labeling	Sample Area (cm^2)	Surface Area (cm^2)	MAC	Less Than or Equal to Limit of Detection	Bio-Burden NMT 33 cfu/25 cm^2	Testing Method
1.		S1	25	32				STM-MC-001
2.		S2	25	32				
3.		S3	25	11				
4.		S4	25	11				
5.		S5	25	11				
6.		S6	25	7.5				
7.		S7	25	7.5				
8.		S8	25	7.5				
9.		S9	25	17.5				
10.		S10	25	8320				
11.		S11	25	8320				
12.		S12	25	9				

Your Company's Logo **Your Company's Name**

Attachment IV

Calculation for Surface Swabs

$$\text{MAC} = \frac{\text{TD} \times \text{BS} \times \text{SF}}{\text{LDD}}.$$

Calculation:

$$Y1 = X \times \text{surface area},$$

where Y is the active ingredient on the corresponding equipment part, X is the active ingredient recovered from 25 cm^2 by swab from the corresponding equipment part, and surface area is the area of the corresponding equipment parts S1–S12.

$$Z = Y1 + Y2 + Y3 + Y4 + Y5 + Y6 + Y7 + Y8 + Y9 + Y10 + Y11 + Y12,$$

where Z is the total active ingredient recovered from the machine, $Y1$ is the active ingredient recovered from part S1, $Y2$ is the active ingredient recovered from part S2, $Y3$ is the active ingredient recovered from part S3, $Y4$ is the active ingredient recovered from part S4, $Y5$ is the active ingredient recovered from part S5, $Y6$ is the active ingredient recovered from part S6, $Y7$ is the active ingredient recovered from part 7, $Y8$ is the active ingredient recovered from part 8, $Y9$ is the active ingredient recovered from part 9, $Y10$ is the active ingredient recovered from part 10, $Y11$ is the active ingredient recovered from part 11, and $Y12$ is the active ingredient recovered from part 12.

Acceptance criteria:

$$Z \leq \text{MAC}.$$

Your Company's Logo **Your Company's Name**

Attachment V

Training Record Verification (Production Staff)

The following staff found trained on cleaning of the equipment.

Using SOP No. ABC-005; Revision No.; Issued on; Date and SOP No. ABC-006; Revision No.; Issued on; Date

Name: _____ ID No.: _____ Sign.: _____ Date: _____

Name: _____ ID No.: _____ Sign.: _____ Date: _____

Training Record Verification (Analyst)

The following analyst trained on STM No. _____

Name: _____ ID No.: _____ Sign.: _____ Date: _____

Performed by: _____ Checked by: _____

Date: _____ Date: _____

Your Company's Logo **Your Company's Name**

Attachment VI

Swab Analysis Results

Sampling Location	Visual Inspection	Detergent Detection (No Foam)	Bio-Burden Test NMT 33 cfu/25 cm^2	Carryover HPLC Result per 25 cm^2 (X)	Carryover 25 cm^2 × Surface Area Total Carryover $Y = X \times$ Surface Area
S1					
S2					
S3					
S4					
S5					
S6					
S7					
S8					
S9					
S10					
S11					
S12					

Your Company's Logo **Your Company's Name**

Attachment VII

Swab Sampling Recovery (Challenge) Test

Name of Active Material	Concentration of Standard Solution	Type of Swab	Total Area of Swab	% Recovery of Active Ingredient	% Recovery as per Limit NLT (70%)	
					Y	N

CLV-20.6

Cleaning Validation Protocol for Sieve

Your Company's Logo

Your Company's Name

ABC Pharmaceutical Company	**CLEANING VALIDATION PROTOCOL** **Equipment Name**	
	Issued on **Date**	**Protocol Number** **CLVS-000**
	Location **ABC Pharmaceutical Company** **(Granulation Area)** **Room No. 000**	

Equipment ..... **Sieve**

Model ..... **Model**

Manufacturer ..... **Company, Country**

Written by	**Signature & Date**
Validation Officer	_____
Reviewed by	**Signature & Date**
QA Manager	_____
	Signature & Date
QC Manager	_____
	Signature & Date
Production Manager	_____
Approved by	**Signature & Date**
Production Director	_____
Authorized by	**Signature & Date**
QA Director	_____

Your Company's Logo **Your Company's Name**

20.6.1 Objective

The objective of this protocol is to demonstrate that the cleaning procedure No. ABC-001 will successfully and consistently reduce the level of residues to a predetermined level of acceptability, so as to prevent contamination (product or cleaning process related) from adversely affecting the safety and quality of the next product manufactured.

20.6.2 Scope

This protocol will cover pre- and postcleaning of the sieve (Figure 20.6.1) for the dry tablet products.

In the grouping matrix, products are divided into various groups based on their

a. Water solubility
b. Therapeutic dosage
c. Toxicity
d. Batch size (in kg)

From each group, one worst-case product is considered for cleaning validation (Table 20.6.1).

20.6.3 Responsibility

The following personnel are responsible for the execution of this protocol:

Validation officer/production officer/QA inspector/QC chemist/analyst/machine operator.

For details, please refer to Attachment II.

20.6.4 Description of the Cleaning Process

The sieve is cleaned manually as per SOP No. ABC-001.

4.1 Remove the label "UNDER CLEANING".
4.2 Release the clamps.

Your Company's Logo **Your Company's Name**

FIGURE 20.6.1
Front view of the sieve.

4.3 Remove the rim/channel gasket, sieve, and sieve deck
4.4 Flush the rim and sieve deck with water
4.5 Clean the rim and sieve deck with a sponge dipped in liquid soap, and flush them with water
4.6 Flush the channel gasket with water
4.7 Clean both sides of the channel gaskets with a sponge dipped in liquid soap, and flush it with water
4.8 Flush the sieve with water
4.9 Clean the sieve with a nylon brush or a sponge dipped in liquid soap, and flush with water
4.10 Blow the sieve with compressed air to remove any powder residue
4.11 Spray all the clean parts with 70% alcohol, and keep them over a clean pallet overnight to dry
4.12 Blow each part with compressed air to dry, if immediate use is required

TABLE 20.6.1
Worst Case for Sieve

Products	Reason for Selecting as Worst Case
Ciprofloxacin 500 mg tablets	Six ingredients are insoluble in water
Ketotifen 1.0 mg tablets	Minimum therapeutic dose (1.0 mg)
Diclofenac 50 mg tablets	LD_{50} 150 mg/kg oral rat
Sulfamethoxazole D/S tablets	Largest batch size (825 kg)

Your Company's Logo **Your Company's Name**

4.13 Clean the body of the machine with a wet towel
4.14 Clean the body of the machine with a towel dipped in liquid soap, followed by a wet towel
4.15 Label the machine "CLEAN"
4.16 Make entries in the cleaning logbook as per SOP

20.6.4.1 Difficult-to-Clean Parts

i. Sieve
ii. Rim
iii. Channel gasket

20.6.5 Description of the Sampling Process

20.6.5.1 Sampling Technique

The surface swab sampling technique is used to take samples from the sieve.

20.6.5.2 Sampling Precautions

Before taking the sample, wear

i. Gloves
ii. Face mask

20.6.5.3 Procedure for Sampling

Samples of the internal surfaces are taken by moistening the swab (ready-made sterile cotton swab) with a suitable solvent (DIW/alcohol–water–alcohol)

Sample a 25-cm^2 area (see Figure 20.6.2) and place the swab in a test tube containing 10 mL of solvent (suitable solvent)

Swab sample from each part of the sieve is collected as per Table 20.6.2.

20.6.5.4 Handling of Samples

i. After collecting swabs samples for MAC, they are kept in the refrigerator.
ii. Swab Samples for the HPLC analysis are collected at the time of manufacturing; analysis should be completed within 24 h from the time of collection.
iii. HPLC samples should be kept at room temperature for at least 2 h before testing.

Your Company's Logo **Your Company's Name**

TABLE 20.6.2

Surface Swabs Sampling Description

Description	Sample Location	Sample ID	Reference
Sieve	Rim left	S1	Figure 20.6.2
	Rim right	S2	
	Channel gasket	S3	
	Sieve upper surface	S4	
	Sieve lower surface	S5	

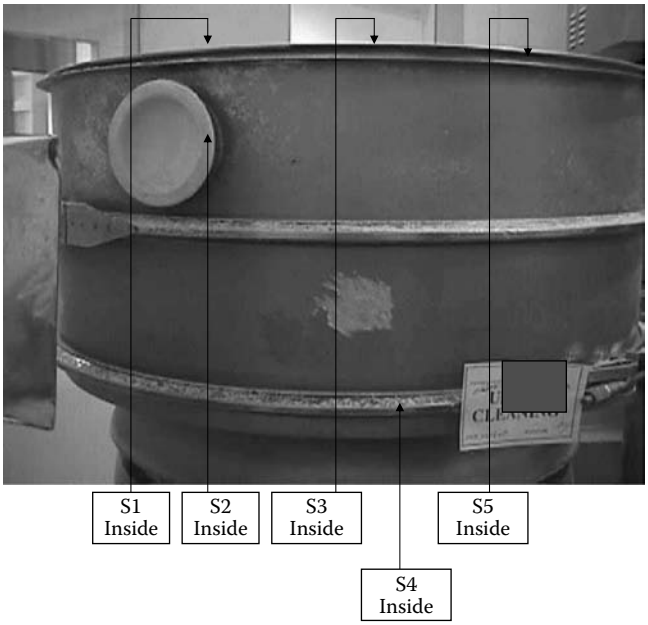


FIGURE 20.6.2
Sampling locations of inside and outside surface of the sieve.

20.6.6 Test Functions

a. *Visual inspection:* Inspection of the sieve is performed visually at the end of the cleaning procedure.

b. *Maximum allowable carryover:* The test for MAC of the swab is performed as per the HPLC method suitable for each product residue.

Notes:

- Analysis will be carried out by pooling the 10 mL swab extraction for specific analysis.

- The validated HPLC test method is used for the determination of chemical residues.

c. *Bio-burden test:* The test for bio-burden is performed as per STM No. MC-0001 by the QC Microbiology section.

d. *Swab recovery challenge test:* The recovery challenge test of the swab sample is performed as per the PDA Guideline.

e. *Detergent detection:* The test for detergent detection should be performed as per procedure No. ABC-003.

20.6.7 Verification of Documents

i. Verify the sieve cleaning procedure.

ii. Verify the sieve cleaning logbook records.

iii. Verify the cleaning operators and analyst training record (refer to Attachment V).

20.6.8 Documentation

i. All analysis results are recorded in the analysis logbook.

ii. Printouts and chromatograms are attached to the validation report and a copy of that is also attached to the analytical logbook.

iii. All analyses and data should be verified by the second analyst.

iv. Cleaning validation officer will check all training records.

v. The final report for cleaning validation is prepared by the validation officer.

20.6.9 Acceptance Criteria

a. *Visual inspection:* The visible internal equipment surfaces and all critical and difficult-to-clean parts are optically free from residue, and the color of the final rinse water is comparable to DIW.

b. *Maximum allowable carryover:* The active ingredient calculated (Z) is either equal to or less than the MAC. Based on the "worst-case" concept

$$Z \leq \text{MAC},$$

$$\text{MAC} = \frac{\text{TD} \times \text{BS} \times \text{SF}}{\text{LDD}},$$

Your Company's Logo **Your Company's Name**

where MAC is the maximum allowable carryover, TD is a single therapeutic dose, BS is the batch size of the next product to be manufactured in the same equipment, SF* is the safety factor (0.001), and LDD is the largest daily dose of the next product to be manufactured in the same equipment.

The calculated value is the maximum amount of active ingredient of a certain product that is allowed to be carried over to the next batch.

Calculation:

$$Y = X \times \text{surface area},$$

where Y is the active ingredient on the corresponding equipment part, X is the active ingredient recovered from 25 cm^2 by swab from the corresponding equipment part, and surface area is the area of corresponding equipment parts A–E.

$$Z = Y1 + Y2 + Y3 + Y4 + Y5$$

where Z is the total active ingredient recovered from the machine, $Y1$ is the active ingredient recovered from part S1, $Y2$ is the active ingredient recovered from part S2, $Y3$ is the active ingredient recovered from part S3, $Y4$ is the active ingredient recovered from part S4, and $Y5$ is the active ingredient recovered from part S5.

Acceptance criteria:

$$Z \leq \text{MAC}.$$

c. *Bio-burden:* The bio-burden should not be more than 33 cfu/25 cm^2 for the swabs.

d. *Swab recovery challenge test:* The swab recovery challenge test should be 70% of the known concentration of standard spiked.

e. *Detergent detection:* No foam was detected on top of the surface after testing.

20.6.10 List of Attachments

Attachment I	Description of equipment and product
Attachment II	Cleaning/testing responsibilities
Attachment III	Sampling and testing plan
Attachment IV	Calculations for surface swabs
Attachment V	Training record verification
Attachment VI	Swabs analysis results
Attachment VII	Swab sampling recovery challenge test results

* 1/100 to 1/1000 of a normal daily dose for oral products (PDA Guideline).

Your Company's Logo **Your Company's Name**

Attachment I

Description of Equipment and Product

Equipment Name: _____

Serial No.: _____

Location: _____

Product Name: _____

Batch No. of the Product: _____

Next Product to Be Manufactured in the Same

Equipment: _____

Manufacturing Date: _____

Active Ingredient: _____

Therapeutic Group: _____

Cleaning Date: _____

Cleaning SOP No.: _____ Revision No.: _____

Sampling Technique: _____ Test Method Reference: _____

Cleaning Sample Analysis Date/Time: _____ Result: _____

Test Method Reference: _____ Reference Analytical Logbook: _____

Limit of Detection: _____

Next Product to be Manufactured in the Same Equipment: _____

Safety Factor: _____

Worst-Case Products

- ☐ Ciprofloxacin 500 mg tablets
- ☐ Ketotifen 1.0 mg tablets
- ☐ Diclofenac 50 mg tablets
- ☐ Sulfamethoxazole D/S tablets

Your Company's Logo **Your Company's Name**

Attachment II

Cleaning/Testing Responsibilities

Cleaning/Testing	Done by	Recorded on	Checked by
Equipment cleaning	Machine operator	Equipment usage/ cleaning logbook	Production supervisor
Visual inspection	Validation officer	Analytical logbook	—
Swab sample	Machine operator/validation officer	Sampling sheet	—
Detergent determination	Validation officer/QC analyst	Analytical logbook	QA/QC officer
MAC	Validation officer/QC analyst	Analytical logbook	QA officer
Bio-burden	Microbiologist	Analytical logbook	Manager QC microbiology
Swab recovery challenge test	QC analyst	Analytical logbook	Senior analyst

Your Company's Logo **Your Company's Name**

Attachment III

Worst-Case Products

- ☐ Ciprofloxacin 500 mg tablets
- ☐ Ketotifen 1.0 mg tablets
- ☐ Diclofenac 50 mg tablets
- ☐ Sulfamethoxazole D/S tablets

Sampling and Testing Plan

S. No.	Visual Inspection	Identification Labeling	Sample Area (cm^2)	Surface Area in Contact with Product (cm^2)	MAC	Less than or Equal to the Limit of Detection	Bio-Burden NMT 33 cfu/25 cm^2	Testing Method
		S1	25	2666				
		S2	25	225				
		S3	25	2666				
		S4	25	8000				
		S5	25	26,666				

Your Company's Logo **Your Company's Name**

Attachment IV

Calculation for Surface Swabs

$$\text{MAC} = \frac{\text{TD} \times \text{BS} \times \text{SF}}{\text{LDD}}$$

Calculation:

$$Y = X \times \text{surface area},$$

where Y is the active ingredient on the corresponding equipment part, X is the active ingredient recovered from 25 cm^2 by swab from the corresponding equipment part, and surface area is the area of corresponding equipment parts A–E.

$$Z = Y1 + Y2 + Y3 + Y4 + Y5,$$

where Z is the total active ingredient recovered from the machine, $Y1$ is the active ingredient recovered from part S1, $Y2$ is the active ingredient recovered from part S2, $Y3$ is the active ingredient recovered from part S3, $Y4$ is the active ingredient recovered from part S4, and $Y5$ is the active ingredient recovered from part S5.

Acceptance criteria:

$$Z \leq \text{MAC}.$$

Your Company's Logo **Your Company's Name**

Attachment V

Training Record Verification (Production Staff)

The following staff found trained on cleaning of the equipment.

Using SOP No. ABC-005; Revision No.; Issued on; Date

Name: _____ ID No.: _____ Sign.: _____ Date: _____

Name: _____ ID No.: _____ Sign.: _____ Date: _____

Training Record Verification (Analyst)

The following analyst trained on STM No. _____

Name: _____ ID No.: _____ Sign.: _____ Date: _____

Performed by: _____ Checked by: _____

Performed by: _____ Checked by: _____

Date: _____ Date: _____

Your Company's Logo **Your Company's Name**

Attachment VI

Worst-Case Products

- ☐ Ciprofloxacin 500 mg tablets
- ☐ Ketotifen 1.0 mg tablets
- ☐ Diclofenac 50 mg tablets
- ☐ Sulfamethoxazole D/S tablets

Swab Analysis Results

Sampling Location	Visual Inspection	Detergent Test	Bio-Burden Test NMT 33 cfu/swab	Carryover HPLC Result per 25 cm^2 (X)	Carryover 25 cm^2 × Surface Area Total Carryover $Y = (X) \times (A - S)$
S1					
S2					
S3					
S4					
S5					

Your Company's Logo **Your Company's Name**

Attachment VII

Swab Sampling Recovery Challenge Test

Name of Active Material	Concentration of Standard Solution	Type of Swab	Total Area of Swab	% Recovery of Active Ingredient	% Recovery as per Limit (70%)	
					Y	N

CLV-20.7

Cleaning Validation Protocol for Powder-Filling Machine

Your Company's Logo

Your Company's Name

ABC Pharmaceutical Company	**CLEANING VALIDATION PROTOCOL** **Equipment Name**	
	Issued on **Date**	**Protocol Number** **CLVS-000**
	Location **ABC Pharmaceutical Company** **(Granulation Area)** **Room No. 000**	

Equipment . . . . . **Powder-filling machine**

Model . . . . . **Model**

Manufacturer . . . . . **Company, Country**

Written by	**Signature & Date**
QA Officer	_____
Reviewed by	**Signature & Date**
Deputy QA Manager Julphar I	_____
	Signature & Date
QC Manager	_____
	Signature & Date
Production Manager	_____
Approved by	**Signature & Date**
Production Director	_____
Authorized by	**Signature & Date**
QA Director	_____

Your Company's Logo **Your Company's Name**

20.7.1 Objective

The objective of this protocol is to demonstrate that the cleaning procedure No. ABC-001 for powder-filling machines will successfully and consistently reduce the level of residues to a predetermined level of acceptability, so as to prevent contamination (product or cleaning process related) from adversely affecting the safety and quality of the next product manufactured.

20.7.2 Scope

This protocol will cover the cleaning process of the powder-filling machine for the granule products.

As per the CVMP grouping matrix, products are divided into various groups based on their

a. Water solubility
b. Therapeutic dosage
c. Toxicity
d. Batch size (in kg)

From each group, one worst-case product is considered for cleaning validation.

However, only two products are manufactured in this category; therefore, both of these products are selected for cleaning validation (Table 20.7.1).

20.7.3 Responsibility

The following personnel are responsible for the execution of this protocol:

Validation officer/production officer/QA inspector/QC chemist/analyst/machine operator.

For details, please refer to Attachment II.

TABLE 20.7.1

Worst Case of PPS Products

Product	Justification for Worst Case
Erythromycin 200 mg/5 mL	Two ingredients that are insoluble in water: Erythrocin (7) Simethicon (7)
Azithromycin 200 mg/5 mL	Largest batch size (200.8 kg)

Your Company's Logo

Your Company's Name

20.7.4 Description of the Cleaning Process

The powder-filling machine (Figure 20.7.1) should be cleaned manually as per SOP No. ABC-001.

4.1 Dismantle the bottle-feed wheel hopper, stirrer, and dosing wormer
4.2 Clean them with a dry duster
4.3 Wash thoroughly with DIW
4.4 Spray 70% ethanol and dry it prior to use
4.5 Clean the conveyor belt and the machine from the outside with a vacuum cleaner to collect the powder
4.6 Use compressed air to remove powder from internal parts of the machine
4.7 Clean with a dry duster followed by a wet duster of 70% ethanol

20.7.4.1 Difficult-to-Clean Parts

i. Powder hopper
ii. Filling nozzle
iii. Powder hopper joint
iv. Turn table

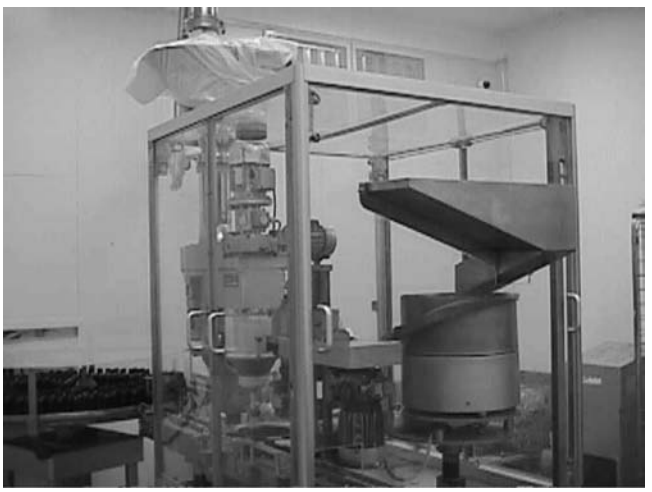


FIGURE 20.7.1
Powder-filling machine.

Your Company's Logo **Your Company's Name**

20.7.5 Description of the Sampling Process

20.7.5.1 Sampling Technique

The surface swab sampling technique should be used to take samples from the powder-filling machine.

20.7.5.2 Procedure for Sampling

Samples of the internal surfaces are taken by moistening the swab (ready-made sterile cotton swab) with a suitable solvent (DIW/alcohol–water–alcohol). Sample a 25-cm^2 area (see Figures 20.7.2 through 20.7.5) and place the swab in a test tube containing 10 mL of solvent (suitable solvent). Swab samples from each part of the powder-filling machine are collected as per Table 20.7.2.

20.7.5.3 Sampling Precautions

Before taking samples, wear

i. Gloves
ii. Face mask

20.7.5.4 Handling of Samples

i. After collecting, keep the swab samples for MAC in the refrigerator.
ii. HPLC samples should be kept at room temperature for at least 2 h before testing starts.

20.7.6 Test Functions

a. *Visual inspection:* Inspection of the powder-filling machine is performed visually after the cleaning procedure.

TABLE 20.7.2

Surface Swabs Sampling Description

Description	Sample Location	Sample ID	Reference
Powder-filling machine	Powder hopper	S1	Figure 20.7.2
	Hopper joints	S2	
	Inner side nozzle	S3	Figure 20.7.3
	Nozzle upper surface	S4	
	Hopper bottom	S5	
	Powder hopper	S6	Figure 20.7.4
	Turn table	S7	Figure 20.7.5
	Machine surface center	S8	
	Conveyer top surface	S9	

Your Company's Logo **Your Company's Name**

FIGURE 20.7.2
Hopper and powder chute sampling location.

b. *Maximum allowable carryover:* The test for MAC of the final swab is performed as per the HPLC method suitable for each product residue.

Notes:

- Analysis will be carried out by pooling the 10 mL swabs extraction for specific analysis.

FIGURE 20.7.3
Dosing wormer bottom and filling nozzle.

Your Company's Logo **Your Company's Name**

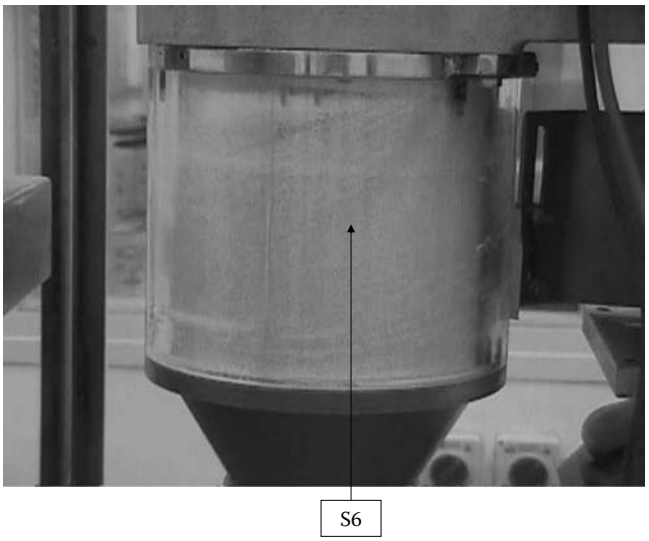


FIGURE 20.7.4
Dosing wormer wall.

- The validated HPLC test method is used for the determination of chemical residues

c. *Bio-burden test:* The test for bio-burden is performed as per STM No. MC-0001 by the QC Microbiology section.

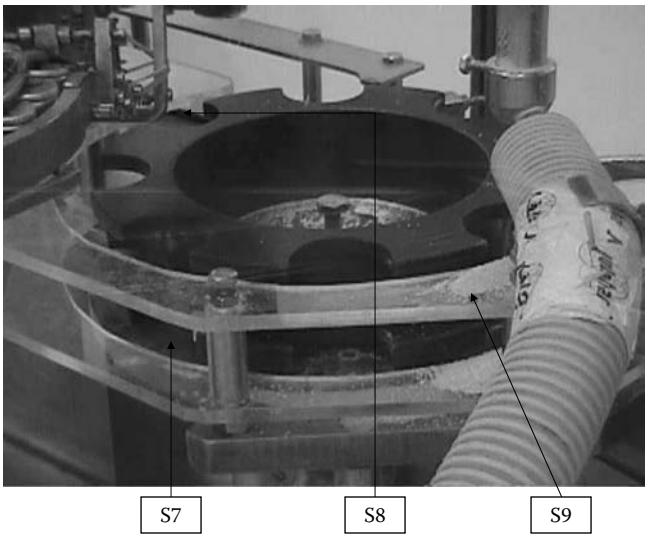


FIGURE 20.7.5
Turn table body surface.

Your Company's Logo **Your Company's Name**

d. *Swab recovery challenge test:* The recovery challenge test is performed for the swab sample.

20.7.7 Verification of Documents

i. Verify the powder-filling machine cleaning procedure.
ii. Verify the powder-filling machine cleaning logbook records.
iii. Verify the staff training record (refer to Attachment V).

20.7.8 Documentation

i. All analysis results are recorded in the analysis logbook.
ii. Printouts and chromatograms are attached to the validation report and a copy of that is also attached to the analytical logbook.
iii. All analyses and data are verified by a second analyst.
iv. The cleaning validation officer will check all training records.
v. The final report for cleaning validation is prepared by the validation officer.

20.7.9 Acceptance Criteria

a. *Visual inspection:* The visible internal equipment surfaces and all critical and difficult-to-clean parts are optically free from visible residues.
b. *Maximum allowable carryover:* The active ingredient calculated (Z) is either equal to or less than the MAC.

$$Z \leq \text{MAC},$$

$$\text{MAC} = \frac{\text{TD} \times \text{BS} \times \text{SF}}{\text{LDD}},$$

where MAC is the maximum allowable carryover, TD is a single therapeutic dose, BS is the batch size of the next product to be manufactured in the same equipment, SF*

* 1/100 to 1/1000 of a normal daily dose for oral products (PDA Guideline).

Your Company's Logo **Your Company's Name**

is the safety factor (0.001), and LDD is the largest daily dose of the next product to be manufactured in the same equipment.

The calculated value is the maximum amount of active ingredient of a certain product that is allowed to be carried over to the next batch.

Calculation:

$$Y = X \times \text{surface area},$$

where Y is the active ingredient on the corresponding equipment part, X is the active ingredient recovered from 25 cm^2 by swab from corresponding equipment part, and surface area is the area of corresponding equipment parts A–I.

$$Z = Y1 + Y2 + Y3 + Y4 + Y5 + Y6 + Y7 + Y8 + Y9,$$

where Z is the total active ingredient recovered from the machine, $Y1$ is the active ingredient recovered from part S1, $Y2$ is the active ingredient recovered from part S2, $Y3$ is the active ingredient recovered from part S3, $Y4$ is the active ingredient recovered from part S4, $Y5$ is the active ingredient recovered from part S5, $Y6$ is the active ingredient recovered from part S6, $Y7$ is the active ingredient recovered from part S7, $Y8$ is the active ingredient recovered from part S8, and $Y9$ is the active ingredient recovered from part S9.

Acceptance criteria:

$$Z \leq \text{MAC}.$$

c. *Bio-burden:* The bio-burden should not be more than 33 cfu/25 cm^2 for the swabs.
d. *Swab recovery challenge test:* The swab recovery challenge test should be 70% of the known concentration of standard spiked.

20.7.10 List of Attachments

Attachment I	Description of equipment and product
Attachment II	Cleaning/testing responsibilities
Attachment III	Sampling and testing plan
Attachment IV	Calculations for surface swabs
Attachment V	Training record verification
Attachment VI	Swabs analysis results
Attachment VII	Swab sampling recovery challenge test results

Your Company's Logo **Your Company's Name**

Attachment I

Description of Equipment and Product

Equipment Name: _____

Serial No.: _____

Validated on: _____

Room No.: _____

Product Name: _____

Worst-Case Products

☐ Erythromycin 200 mg/5 mL

☐ Azithromycin 200 mg/5 mL

Next Product to Be Manufactured in the Same Equipment: _____

Manufacturing Date: _____

Active Ingredient: _____

Therapeutic Group: _____

Cleaning Date: _____

Cleaning SOP No.: _____ Revision No.: _____

Sampling Technique: _____ Test Method Reference: _____

Cleaning Sample Analysis Date/Time: _____ Result: _____

Test Method Reference: _____ Reference Analytical Logbook: _____

_____

Limit of Detection: _____

Next Product to be Manufactured in the Same Equipment: _____

Safety Factor: _____

Your Company's Logo **Your Company's Name**

Attachment II

Worst-Case Products

☐ Erythromycin 200 mg/5 mL

☐ Azythromycin 200 mg/5 mL

Cleaning/Testing Responsibilities

Cleaning/Testing	Done by	Recorded on	Checked by
Equipment cleaning	Machine operator	Equipment usage/ cleaning logbook	Production supervisor
Visual inspection	Validation officer	Analytical logbook	—
Swab sample	Machine operator/validation officer	Sampling sheet	Validation officer
MAC	Validation officer/QC analyst	Analytical logbook	QC officer
Bio-burden	Microbiologist	Analytical logbook	Assistant manager QC, microbiology
Swab recovery challenge test	Analyst	Analytical logbook	Senior analyst

Your Company's Logo **Your Company's Name**

Attachment III

Worst-Case Products

☐ Erythromycin 200 mg/5 mL

☐ Azythromycin 200 mg/5 mL

Sampling and Testing Plan

S. No.	Visual Inspection	Identification Labeling	Sample Area (cm^2)	Surface Area in Contact with Product (cm^2)	MAC	Less than or Equal to the Limit of Detection	Bio-Burden NMT 33 cfu/ 25 cm^2	Testing Method
		S1	25	3306				STM-MC-001
		S2	25	144				
		S3	25	1				
		S4	25	2.3				
		S5	25	225				

Your Company's Logo **Your Company's Name**

Attachment IV

Worst-Case Products

☐ Erythromycin 200 mg/5 mL

☐ Azythromycin 200 mg/5 mL

Calculation for Surface Swabs

$$\text{MAC} = \frac{\text{TD} \times \text{BS} \times \text{SF}}{\text{LDD}}.$$

Calculation:

$$Y = X \times \text{surface area},$$

where Y is the active ingredient on the corresponding equipment part, X is the active ingredient recovered from 25 cm^2 by swab from the corresponding equipment part, and surface area is the area of corresponding equipment parts S1–S9.

$$Z = Y1 + Y2 + Y3 + Y4 + Y5 + Y6 + Y7 + Y8 + Y9,$$

where Z is the total active ingredient recovered from the machine, $Y1$ is the active ingredient recovered from part S1, $Y2$ is the active ingredient recovered from part S2, $Y3$ is the active ingredient recovered from part S3, $Y4$ is the active ingredient recovered from part S4, $Y5$ is the active ingredient recovered from part S5, $Y6$ is the active ingredient recovered from part S5, $Y7$ is the active ingredient recovered from part S7, $Y8$ is the active ingredient recovered from part S8, and $Y9$ is the active ingredient recovered from part S9.

Acceptance criteria:

$$Z \leq \text{MAC}.$$

Your Company's Logo **Your Company's Name**

Attachment V

Worst-Case Products

☐ Erythromycin 200 mg/5 mL

☐ Azythromycin 200 mg/5 mL

Training Record Verification (Production Staff)

The following staff found trained on cleaning of the equipment.

Using SOP No. ABC-006; Revision No.; Issued on; Date

Name: _____ ID No.: _____ Sign.: _____ Date: _____

Name: _____ ID No.: _____ Sign.: _____ Date: _____

Training Record Verification (Analyst)

The following analyst trained on STM No.: _____

Name: _____ ID No.: _____ Sign.: _____ Date: _____

Performed by: _____ Checked by: _____

Date: _____ Date: _____

Your Company's Logo **Your Company's Name**

Attachment VI

Worst-Case Products

☐ Erythromycin 200 mg/5 mL

☐ Azythromycin 200 mg/5 mL

Swab Analysis Results

Sampling Location	Visual Inspection	Bio-Burden Test NMT 33 cfu/swab	Carryover HPLC Result per 25 cm^2 (X)	Carryover 25 cm^2 × Surface Area Total Carryover $Y = X \times (A–S)$
S1				
S2				
S3				
S4				
S5				
S6				
S7				
S8				
S9				

Your Company's Logo **Your Company's Name**

Attachment VII

Swab Sampling Recovery (Challenge) Test

Name of Active Material	Concentration of Standard Solution	Type of Swab	Total Area of Swab	% Recovery of Active Ingredient	% Recovery as per Limit NLT (70%)	
					Y	N

CLV-20.8

Cleaning Validation Protocol for Encapsulation Machine

Your Company's Logo **Your Company's Name**

ABC Pharmaceutical Company	**CLEANING VALIDATION PROTOCOL** **Equipment Name**	
	Issued on **Date**	**Protocol Number** **CLVS-000**
	Location **Encapsulation Area** **Room No. 000**	

Equipment.....Capsule-filling machine

Model.....Make and model

Manufacturer .....Company, Country

20.8.1 Cleaning Validation Protocol for Encapsulation Machine (Type A)

20.8.1.1 Objective

The objective of this protocol is to demonstrate that the cleaning procedure No. ABC-001 will successfully and consistently reduce the level of residues to a predetermined level of acceptability, so as to prevent contamination (product or cleaning process related) from adversely affecting the safety and quality of the next product manufactured.

20.8.1.2 Scope

This protocol will cover pre- and postcleaning of the capsule-filling machine type A for the capsule products (Figure 20.8.1.1).

In the grouping matrix, products are divided into various groups based on their

a. Water solubility
b. Therapeutic dosage

Your Company's Logo **Your Company's Name**

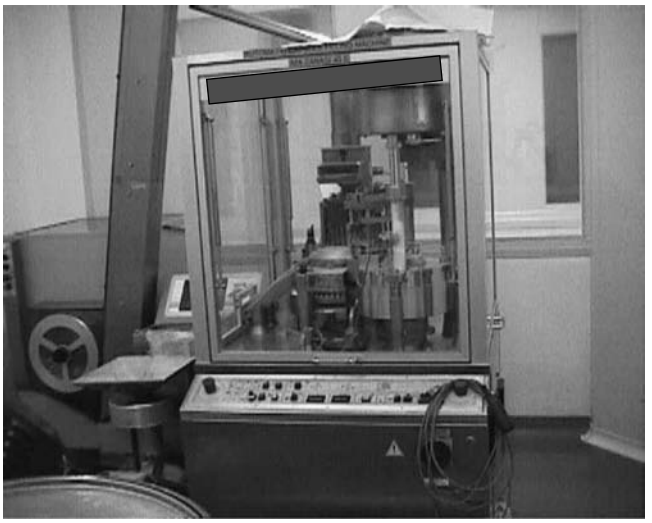


FIGURE 20.8.1.1
Capsulation machine type A.

c. Toxicity
d. Batch size

From each group, one worst-case product is considered for cleaning validation. The following capsule products are encapsulated using this machine:

- Indomethacin 25 mg capsule
- Tetracycline 250 mg capsule
- Oxytetracycline 250 mg capsule
- Doxicycline 100 mg capsule
- Fluoxetine 20 mg capsule
- Azythromycin capsule

The worst-case products among the above-mentioned products are as shown in Table 20.8.1.1.

20.8.1.3 Responsibility

The following personnel are responsible for the execution of this protocol:

Validation officer/productionluf officer/QA inspector/QC chemist/machine operator.

For details, please refer to Attachment II.

Your Company's Logo **Your Company's Name**

TABLE 20.8.1.1

Worst-Case Products of Capsulation Machine

Products	Reason for Selecting as Worst Case
Oxyteracycline 250 mg	Three ingredients that are insoluble in water: Aerosil 200 (7) Magnesium stearate (7) Talc fine (7)
Fluoxetine 20 mg	Minimum therapeutic dose (20 mg)
Oxytetracycline 250 mg	LD_{50} 680 mg/kg oral rat
Indomethacin 25 mg	Largest batch size (1,000,000)

20.8.1.4 Description of the Cleaning Process

Capsule-filling machine ABC encapsulator will be cleaned manually as per SOP No. ABC-001.

4.1 Label the machine "UNDER CLEANING" as per SOP No. ABC-002

4.2 Open the machine door

4.3 Remove the powder and empty capsules from the hoppers

4.4 Clean the inside of the machine removing powder and capsules by means of vacuum

4.5 Dismantle the powder hopper, capsule hopper, plastic pipe, powder receiver, sigments, and filling nozzle and keep them on a trolley

4.6 Wash these parts with water and dry them with compressed air

4.7 Clean the inside of the machine, outside doors of the machine, sorting machine, and check master with a clean wet towel

4.8 Open the dust collector, remove the powder from inside, and wash the powder receiver with water

4.9 Clean the dust collector from outside and the hoses with a wet towel free from dust

4.10 Assemble the machine if required as per SOP No. ABC-003

4.11 Label the machine "CLEAN"

4.12 Make entries in the cleaning, maintenance, and usage logbooks as per SOP No. ABC-004.

20.8.1.5 Description of the Sampling Process

20.8.1.5.1 Sampling Technique

The swab sampling technique is used to take samples from the capsule-filling machine.

Your Company's Logo

Your Company's Name

20.8.1.5.2 Sampling Precautions

Before taking the sample, wear the following:

i. Gloves
ii. Face mask

20.8.1.5.3 Procedure for Sampling

Samples of the internal surfaces are taken by moistening the swab (ready-made sterile cotton swab) with a suitable solvent (DIW/alcohol–water–alcohol). Sample a 25-cm^2 area (see Figures 20.8.1.2 through 20.8.1.5) and place the swab in a test tube containing 10 mL of solvent (suitable solvent). Swab samples from each part of the capsule-filling machine are collected as per Table 20.8.1.2.

20.8.1.5.4 Handling of Samples

i. After collecting swab samples for MAC, they are kept in the refrigerator.
ii. Swabs samples for the HPLC analysis collected at the time of manufacturing analysis should be completed within 24 h from the time of collection.
iii. HPLC samples should be kept at room temperature for at least 2 h before testing.

TABLE 20.8.1.2

Surface Swabs Sampling Description

Description	Sample Location	Sample ID	Reference
Capsule-filling machine	Disc top surface	S1	Figure 20.8.1.2
	Disc right surface	S2	
	Disc bottom surface	S3	
	Capsule channel-1	S4	Figure 20.8.1.3
	Capsule channel-2	S5	
	Capsule channel-3	S6	
	Capsule channel-4	S7	
	Capsule channel-5	S8	
	Capsule channel-6	S9	
	Capsule hopper left	S10	Figure 20.8.1.4
	Capsule hopper center	S11	
	Capsule hopper right	S12	
	Capsule tray left	S13	Figure 20.8.1.5
	Capsule tray center	S14	
	Capsule tray right	S15	
	Filling nozzle-1	S16	—
	Filling nozzle-2	S17	

Your Company's Logo **Your Company's Name**

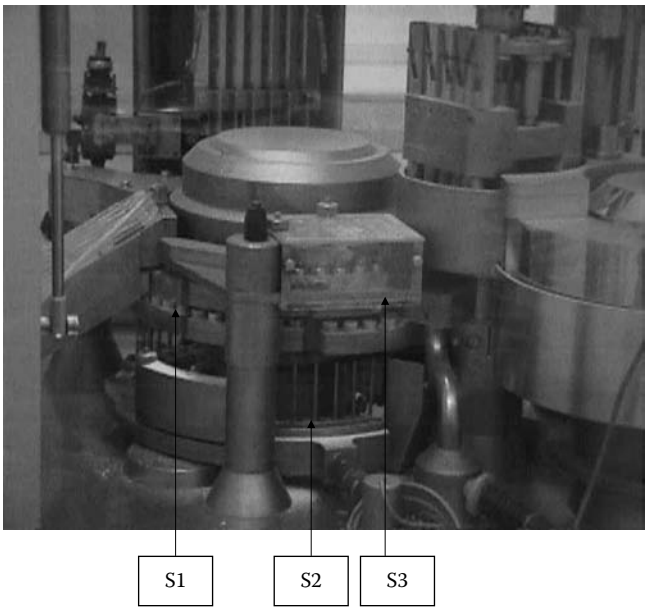


FIGURE 20.8.1.2
Capsule machine disc and capsule hopper.

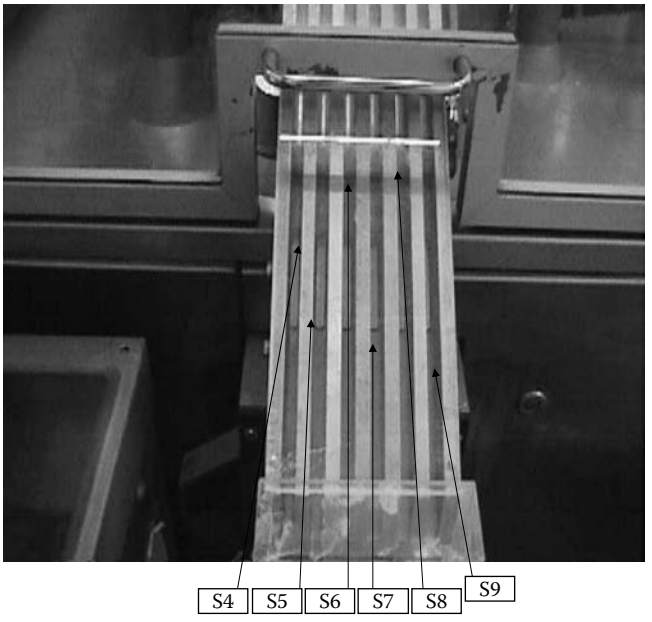


FIGURE 20.8.1.3
Capsule channels.

Your Company's Logo **Your Company's Name**

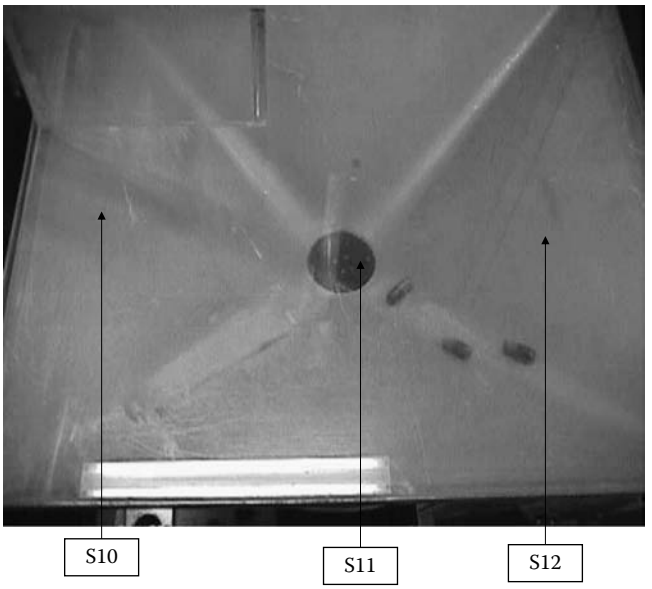


FIGURE 20.8.1.4
Capsule hopper.

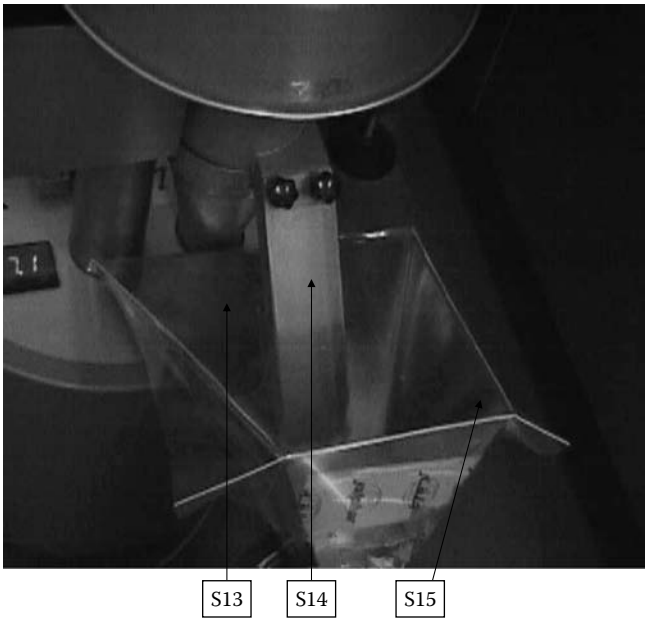


FIGURE 20.8.1.5
Capsule tray.

Your Company's Logo **Your Company's Name**

20.8.1.6 Test Functions

a. *Visual inspection:* Inspection of the capsule-filling machine is performed visually, at the end of the cleaning procedure.
b. *Maximum allowable carryover:* The test for MAC of the final rinse/swab is performed as per the HPLC method suitable for each product residue.

   Notes:

   - Analysis will be carried out by pooling the 10 mL swab extraction for specific analysis.
   - The validated HPLC test method is used for the determination of chemical residues.

c. *Bio-burden test:* The test for bio-burden is performed as per STM No. MC-0001 by the Microbiology section.
d. *Swab recovery challenge test:* The recovery challenge test should be performed of the swab sample as per the PDA Guideline.

20.8.1.7 Verification of Documents

i. Verify the capsule-filling machine cleaning procedure.
ii. Verify the capsule-filling machine cleaning logbook records.
iii. Verify the cleaning operators and analyst training records (refer to Attachment V).

20.8.1.8 Documentation

i. All analyses results are recorded in the analysis logbook.
ii. Printouts and chromatograms are attached to the validation report and a copy of that is also attached to the analytical logbook.
iii. All analyses and data should be verified by the second analyst.
iv. Cleaning validation officer will check all training records.
v. The final report for cleaning validation is prepared by the validation assurance officer.

20.8.1.9 Acceptance Criteria

a. *Visual inspection:* The visible internal equipment surfaces and all critical and difficult-to-clean parts are optically free from visible residues.
b. *Maximum allowable carryover:* The active ingredient calculated (Z) is either equal to or less than the MAC.

$$Z \leq \text{MAC},$$

Your Company's Logo **Your Company's Name**

$$\text{MAC} = \frac{\text{TD} \times \text{BS} \times \text{SF}}{\text{LDD}},$$

where MAC is the maximum allowable carryover, TD is a single therapeutic dose, BS is the batch size of the next product to be manufactured in the same equipment, SF* is the safety factor (0.001), and LDD is the largest daily dose of the next product to be manufactured in the same equipment.

The calculated value is the maximum amount of active ingredient of worst-case product that is allowed to be carried over to the next batch.

Calculation:

$$Y = X \times \text{surface area},$$

where Y is the active ingredient on the corresponding equipment part, X is the active ingredient recovered from 25 cm^2 by swab from the corresponding equipment part, and surface area is the area of corresponding equipment parts A–O.

$$Z = Y1 + Y2 + Y3 + Y4 + Y5 + Y6 + Y7 + Y8 + Y9 + Y10 + Y11 + Y12 + Y13 + Y14 + Y15,$$

where Z is the total active ingredient recovered from the machine, $Y1$ is the active ingredient recovered from part S1, $Y2$ is the active ingredient recovered from part S2, $Y3$ is the active ingredient recovered from part S3, $Y4$ is the active ingredient recovered from part S4, $Y5$ is the active ingredient recovered from part S5, $Y6$ is the active ingredient recovered from part S6, $Y7$ is the active ingredient recovered from part S7, $Y8$ is the active ingredient recovered from part S8, $Y9$ is the active ingredient recovered from part S9, $Y10$ is the active ingredient recovered from part S10, $Y11$ is the active ingredient recovered from part S11, $Y12$ is the active ingredient recovered from part S12, $Y13$ is the active ingredient recovered from part S13, $Y14$ is the active ingredient recovered from part S14, and $Y15$ is the active ingredient recovered from part S15.

Acceptance criteria:

$$Z \leq \text{MAC}.$$

c. *Bio-burden:* The bio-burden should not be more than 33 cfu/25 cm^2 for the swabs.

d. *Swab recovery challenge test:* The swab recovery challenge test should be 70% of the known concentration of standard spiked.

* 1/100 to 1/1000 of a normal daily dose for oral products (PDA Guideline).

Your Company's Logo **Your Company's Name**

20.8.1.10 List of Attachments

Attachment I	Description of equipment and product
Attachment II	Cleaning/testing responsibilities
Attachment III	Sampling and testing plan
Attachment IV	Calculations for surface swabs
Attachment V	Training record verification
Attachment VI	Swabs analysis results
Attachment VII	Swab sampling recovery challenge test results

Your Company's Logo **Your Company's Name**

Attachment I

Description of Equipment and Product

Equipment Name: _____

Serial No.: _____

Capacity: _____

Room No.: _____

Product Name: _____

Batch No. of the Product: _____

Worst-Case Products

- ☐ Oxytetracyclin 250 mg
- ☐ Fluoxitin 2.0 mg
- ☐ Indomethacin 25 mg

Next Product to Be Manufactured in the Same Equipment: _____

Manufacturing Date: _____

Active Ingredient: _____

Therapeutic Group: _____

Cleaning Date: _____

Cleaning SOP No.: _____ Revision No.: _____

Sampling Technique: _____

Cleaning Sample Analysis Date/Time: _____ Result: _____

Test Method Reference: _____ Reference Analytical Logbook: _____

Limit of Detection: _____

Safety Factor: _____

Your Company's Logo **Your Company's Name**

Attachment II

Cleaning/Testing Responsibilities

Cleaning/Testing	Done by	Recorded on	Checked by
Equipment cleaning	Machine operator	Equipment usage/ cleaning logbook	Production supervisor
Visual inspection	Validation officer	Analytical logbook	—
Swab sample	Machine operator/ validation officer	Sampling sheet	QA officer
Detergent determination	Validation officer/QC analyst	Analytical logbook	QA/QC officer
MAC	Validation officer/QC analyst	Analytical logbook	QC officer
Bio-burden	Microbiologist	Analytical logbook	Assistant manager QC, Microbiology
Swab recovery challenge test	Analyst	Analytical logbook	Senior analyst

Your Company's Logo **Your Company's Name**

Attachment III

Worst-Case Products

- ☐ Oxytetracyclin 250 mg
- ☐ Fluoxitin 20 mg
- ☐ Indomethacin 25 mg

Sampling and Testing Plan

S. No.	Visual Inspection	Identification Labeling	Sample Area (cm^2)	Surface Area (cm^2)	Maximum Allowable Carryover (MAC)	Less Than or Equal to Limit of Detection	Bio-Burden NMT 33 cfu/25 cm^2	Testing Method
		S1	25					STM-MC-001
		S2	25					
		S3	25					
		S4	25	12				
		S5	25	12				
		S6	25	12				
		S7	25	12				
		S8	25	12				
		S9	25	12				
		S10	25	703				
		S11	25	3				
		S12	25	703				
		S13	25	350				
		S14	25	5				
		S15	25	350				

Your Company's Logo **Your Company's Name**

Attachment IV

Calculation for Surface Swabs

$$\text{MAC} = \frac{\text{TD} \times \text{BS} \times \text{SF}}{\text{LDD}}.$$

Calculation:

$$Y1 = X \times \text{Surface area},$$

where Y is the active ingredient on the corresponding equipment part, X is the active ingredient recovered from 25 cm^2 by swab from the corresponding equipment part, surface area is the area of corresponding equipment parts A–O.

$$Z = Y1 + Y2 + Y3 + Y4 + Y5 + Y6 + Y7 + Y8 + Y9 + Y10 + Y11 + Y12 + Y13 + Y14 + Y15,$$

where Z is the total active ingredient recovered from the machine, $Y1$ is the active ingredient recovered from part S1, $Y2$ is the active ingredient recovered from part S2, $Y3$ is the active ingredient recovered from part S3, $Y4$ is the active ingredient recovered from part S4, $Y5$ is the active ingredient recovered from part S5, $Y6$ is the active ingredient recovered from part S6, $Y7$ is the active ingredient recovered from part S7, $Y8$ is the active ingredient recovered from part S8, $Y9$ is the active ingredient recovered from part S9, and $Y10$ is the active ingredient recovered from part S10, $Y10$ is the active ingredient recovered from part S11, $Y12$ is the active ingredient recovered from part S12, $Y13$ is the active ingredient recovered from part S13, $Y14$ is the active ingredient recovered from part S14, $Y15$ is the active ingredient recovered from part S15.

Acceptance criteria:

$$Z \leq \text{MAC}.$$

Your Company's Logo **Your Company's Name**

Attachment V

Training Record Verification (Production Staff)

The following staff found trained on cleaning of the equipment.

Using SOP No. ABC-005; Revision No.; Issued on; Date

Name: _____ ID No.: _____ Sign.: _____ Date: _____

Name: _____ ID No.: _____ Sign.: _____ Date: _____

Training Record Verification (Analyst)

The following analyst trained on STM No.: _____

Name: _____ ID No.: _____ Sign.: _____ Date: _____

Performed by: _____ Checked by: _____

Date: _____ Date: _____

Your Company's Logo **Your Company's Name**

Attachment VI

Worst-Case Products

- ☐ Oxytetracyclin 250 mg
- ☐ Fluoxitin 20 mg
- ☐ Indomethacin 25 mg

Swab Analysis Results

Sampling Location	Visual Inspection	Bio-Burden Test: NMT 33 cfu/25 cm^2	Carryover HPLC Result per 25 cm^2 (X)	Carryover 25 cm^2 × Surface Area Total Carryover $Y = X \times$ Surface Area
S1				
S2				
S3				
S4				
S5				
S6				
S7				
S8				
S9				
S10				
S11				
S12				
S13				
S14				
S15				

Your Company's Logo **Your Company's Name**

Attachment VII

Swab Sampling Recovery (Challenge) Test

Name of Active Material	Concentration of Standard Solution	Type of Swab	Total Area of Swab	% Recovery of Active Ingredient	% Recovery as per Limit NLT (70%)	
					Y	N

Your Company's Logo

Your Company's Name

20.8.2 Cleaning Validation Protocol for Encapsulation Machine (Type B)

20.8.2.1 Objective

The objective of this protocol is to demonstrate that the cleaning procedure No. PEC-091 will successfully and consistently reduce the level of residues to a predetermined level of acceptability, so as to prevent contamination (product or cleaning process related) from adversely affecting the safety and quality of the next product manufactured, for the capsule-filling machine.

20.8.2.2 Scope

This protocol will cover the cleaning process of the capsule-filling machine.
Matrix products are divided into various groups based on their

a. Water solubility
b. Therapeutic dosage
c. Toxicity
d. Batch size

Products that were loaded on this machine are as follows (Table 20.8.2.1):

- Omeprazole capsules
- Lansoprazole capsules
- Erythromycin capsules
- Diclofenac retard capsules
- Theophylline capsules
- Ferrous sulfate capsules
- Fluzal capsules

TABLE 20.8.2.1

Worst-Case Products for Encapsulation Machine Type B

Products	Reason for Selecting as Worst Case
Erythromycin 250 mg	Insoluble in water (7)
Lansoprazole 30 mg	Minimum therapeutic dose (30 mg)
Diclofenac 100 mg	LD_{50} 150 mg/kg oral rat
Ferrous sulfate capsule	Largest batch size (1,000,000)

Your Company's Logo **Your Company's Name**

20.8.2.3 Responsibility

The following personnel are responsible for the execution of this protocol:

QA officer/production officer/QA inspector/QC chemist/analyst/machine operator.

For details, please refer to Attachment II.

20.8.2.4 Description of the Cleaning Process

Capsule-filling machine is cleaned manually as per SOP No. ABC-001.

i. Label the machine "UNDER CLEANING" as per SOP No. ABC-002.
ii. Open the machine doors.
iii. Remove the pellets and empty capsule from the hoppers.
iv. Clean the inside of the machine removing pellets and capsules by means of vacuum.
v. Dismantle the pellet hopper, capsule hopper, plastic pipe, pellet receiver, segments, and filling nozzles and keep them on a trolley.
vi. Wash these parts with water and dry them with compressed air.
vii. Clean the inside of the machine, doors, outside of the machine, sorting machine, and check master with a clean wet towel.
viii. Open the dust collector, remove the powder from inside, and wash the powder receiver with water.
ix. Clean the dust collector from outside and hose with a wet towel free from dust.
x. Assemble the machine as per SOP No. ABC-003.
xi. Label the machine with "CLEAN" label.
xii. Make entry in cleaning and maintenance usage logbook as per SOP No. ABC-004.

20.8.2.4.1 Cleaning Agent/Disinfectant

i. Concentration used: _____
ii. Type/nature: _____
iii. pH: _____
iv. Conductivity: _____

20.8.2.5 Description of the Sampling Process

20.8.2.5.1 Sampling Technique

The surface swab technique will be used to take samples from the capsule-filling machine as per SOP No. ABC-005.

Your Company's Logo

Your Company's Name

20.8.2.5.2 Sampling Precautions

For sampling, wear

i. Gloves
ii. Face mask

20.8.2.5.3 Surface Swab

20.8.2.5.3.1 Procedure for Sampling

Samples for the internal surfaces are taken by moistening the swab (ready-made sterile cotton swab) with a suitable solvent (DIW/alcohol–water–alcohol)

Sample a 25-cm^2 area (Ref. Figures 1, 2, 3, 4, 5, 6, 7, and 8) and place the swab in a test tube containing 10 mL of solvent (suitable solvent)

Swab samples are collected as per Table 20.8.2.2.

TABLE 20.8.2.2

Surface Swab Sampling Description

Description	Sample Location	Sample ID	Reference
Pellet hopper	Inner surface	S1	Figure 20.8.2.1 Attachment IVa
Filling machine base	Left surface	S2	Figure 20.8.2.2 Attachment IVb
Filling machine base	Right surface	S3	Figure 20.8.2.2 Attachment IVb
Capsule tray	Inner surface	S4	Figure 20.8.2.3 Attachment IVc
Capsule hopper	Inner surface	S5	Figure 20.8.2.4 Attachment IVd
Capsule channel 1 (Left)	Surface	S6	Figure 20.8.2.5 Attachment IVe
Capsule channel 2 (Right)	Surface	S7	Figure 20.8.2.5 Attachment IVe
Capsule receiving hopper (location 1)	Right outer surface	S8	Figure 20.8.2.6 Attachment IVf
Capsule receiving hopper (location 2)	Middle inner surface	S9	Figure 20.8.2.6 Attachment IVf
Capsule receiving hopper (location 3)	Left outer surface	S10	Figure 20.8.2.6 Attachment Ivf
Filling nozzle (1)	Inner surface	S11	Figure 20.8.2.7 Attachment IVg
Filling nozzle (2)	Outer surface	S12	Figure 20.8.2.7 Attachment IVg
Outlet capsule tray	Surface	S13	Figure 20.8.2.8 Attachment IVh

Your Company's Logo

Your Company's Name

20.8.2.5.4 Handling of Samples

i. Samples should be kept in the refrigerator, if not testing immediately.
ii. HPLC analysis should be completed within 24 h of collection.
iii. HPLC samples should be kept at room temperature for at least 2 h before testing starts.

20.8.2.6 Test Functions

a. *Visual inspection:* Inspection of capsule-filling machine is performed visually at the end of the cleaning procedure.
b. *Maximum allowable carryover:* The test for the MAC of the swab is performed as per the HPLC method suitable for each worst-case product residue.

   Notes:

   - Analysis is carried out by pooling the 10 mL swab extraction for specific analysis.
   - The validated HPLC test method is used for the determination of chemical residues.

c. *Bio-burden test:* The test for bio-burden is performed as per STM No. MC-001 by the QC Microbiology section.
d. *Swab recovery challenge test:* The recovery challenge test of the swab sample is performed as per PDA *Journal of Pharmaceutical Science and Technology*.

20.8.2.7 Verification of Documents

i. Machine logbook
ii. Printouts and chromatogram
iii. Training record
iv. Report/protocol cleaning validation

20.8.2.8 Documentation

i. All analysis results are recorded in the analysis logbook.
ii. Printouts and chromatograms are attached to the validation report and a copy of that is also attached to the analytical logbook.
iii. All analyses and data should be verified by the second analyst.
iv. The cleaning validation officer will check all training records.
v. The final report for cleaning validation should be prepared by the cleaning validation officer.

Your Company's Logo **Your Company's Name**

20.8.2.9 Acceptance Criteria

a. *Visual inspection:* The visible internal equipment surfaces and all critical and difficult-to-clean parts are optically free from residue and the color of the final rinse water is comparable to DIW as per SOP No. ABC-006.

b. *Maximum allowable carryover:* The active ingredient in the swabs is either not detected or equal to or less than the MAC (calculated theoretically for each product).

Formula:

$$\text{MAC} = \frac{\text{TD} \times \text{BS} \times \text{SF}}{\text{LDD}},$$

where MAC is the maximum allowable carryover, TD is a single therapeutic dose, BS is the batch size of the next product to be manufactured in the same equipment, SF* is the safety factor (0.001), and LDD is the largest daily dose of the next product to be manufactured in the same equipment.

c. *Bio-burden:* The bio-burden should not be more than 33 cfu/25 cm^2 for the swabs.

d. *Swab recovery challenge test:* The swab recovery challenge test should be NLT 70% of the known concentration of standard spiked.

20.8.2.10 List of Attachments

Attachment I	Description of equipment and product
Attachment II	Cleaning/testing responsibilities
Attachment III	Sampling and testing plan
Attachment IV	Equipment pictures and sampling locations
Attachment V	Calculations for surface swabs
Attachment VI	Swab analysis result
Attachment VII	Swab sampling recovery challenge test
Attachment VIII	Training record verification

* 1/100 to 1/1000 of a normal daily dose for oral products (PDA Guideline).

Your Company's Logo **Your Company's Name**

Attachment I

Description of Equipment and Product

Equipment Name: _____

Serial No.: _____

Room No.: _____

Product Name: _____

Batch No. of the Product: _____

Worst-Case Products

- ☐ Lansoprazole 30 mg capsule
- ☐ Erythromycin 250 mg
- ☐ Ferrous sulfate capsule
- ☐ Diclofenac 100 mg

Next Product to Be Manufactured in the Same Equipment: _____

Manufacturing Date: _____

Active Ingredient: _____

Therapeutic Group: _____

Cleaning Date: _____

Cleaning SOP No.: _____ Revision No.: _____

Sampling Technique: _____

Cleaning Sample Analysis Date/Time: _____ Result: _____

Test Method Reference: _____ Reference Analytical Logbook: _____

Limit of Detection: _____

Safety Factor: _____

Your Company's Logo **Your Company's Name**

Attachment II

Cleaning/Testing Responsibilities

Cleaning/Testing	Done by	Recorded on	Checked by
Equipment cleaning	Machine operator	Equipment usage/ cleaning logbook	Production supervisor
Visual inspection	Validation officer	Analytical logbook	—
Swab sample	Machine operator/ validation officer	Sampling sheet	—
MAC	Validation officer/QC analyst	Analytical logbook	QC officer
Bio-burden	Microbiologist	Analytical logbook	QC assistant manager, Microbiology
Swab recovery challenge test	Analyst	Analytical logbook	Senior analyst

Your Company's Logo **Your Company's Name**

Attachment III

Worst-Case Products

- ☐ Lansoprazole 30 mg capsule
- ☐ Erythromycin 250 mg
- ☐ Ferrous sulfate capsule
- ☐ Diclofenac 100 mg

Sampling and Testing Plan

Process description: Cleaning (Manual)
Process involved: ABC-001

Sampling Location	Visual Inspection	Identification Labeling	Sample Area (cm^2)	Surface Area (cm^2)	MAC	Less Than or Equal to the Limit of Detection	Bio–Burden NMT 33 cfu/25 cm^2	Testing Method
Pellet hopper		S1	25	12				
Machine base (right)		S2	25	3300				
Machine base (left)		S3	25	3300				
Capsules tray		S4	25	36				
Capsule hopper		S5	25	525				
Capsule channel (left)		S6	25	12				
Capsule channel (right)		S7	25	12				
Capsule receiving hopper location 1		S8	25	706				
Capsule receiving hopper location 2		S9	25	3				
Capsule receiving hopper location 3		S10	25	706				
Filling nozzle 1		S11	25	4				
Filling nozzle 2		S12	25	4				
Capsule tray		S13	25	80				

Your Company's Logo **Your Company's Name**

Attachment IVa

Equipment Figure and Sampling Locations

Capsule (Pellets)-Filling Machine

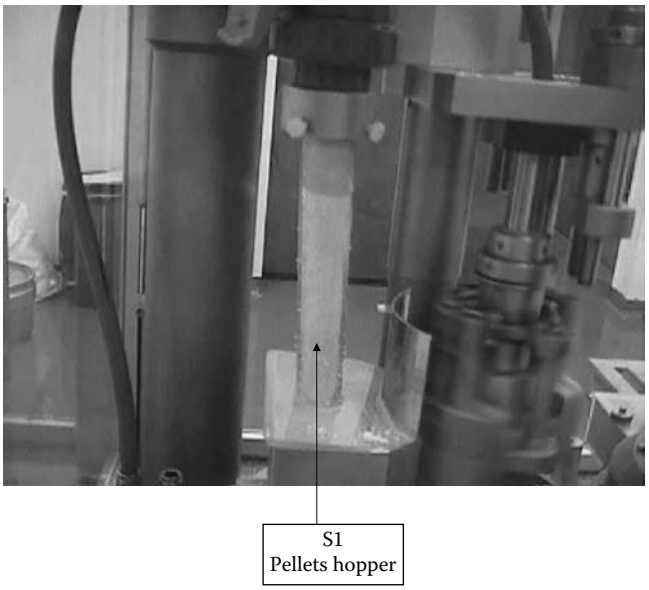


FIGURE 20.8.2.1
Capsule-filling machine pellets hopper.

Your Company's Logo **Your Company's Name**

Attachment IVb

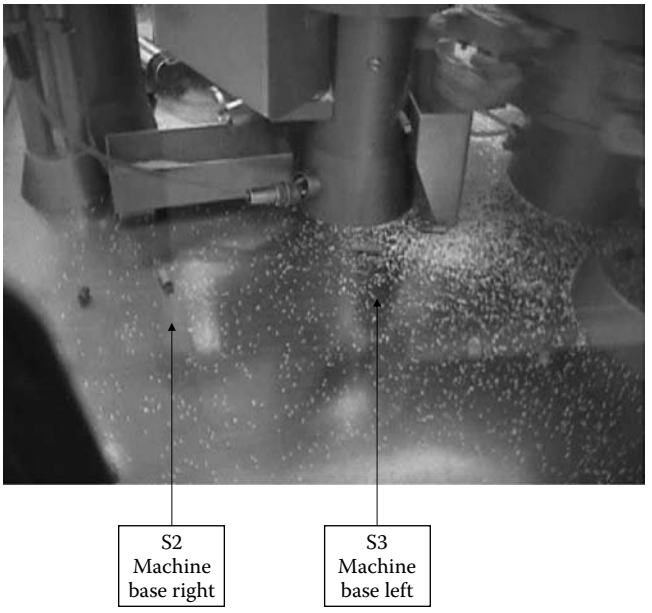


FIGURE 20.8.2.2
Capsule-filling machine's base.

Your Company's Logo **Your Company's Name**

Attachment IVc

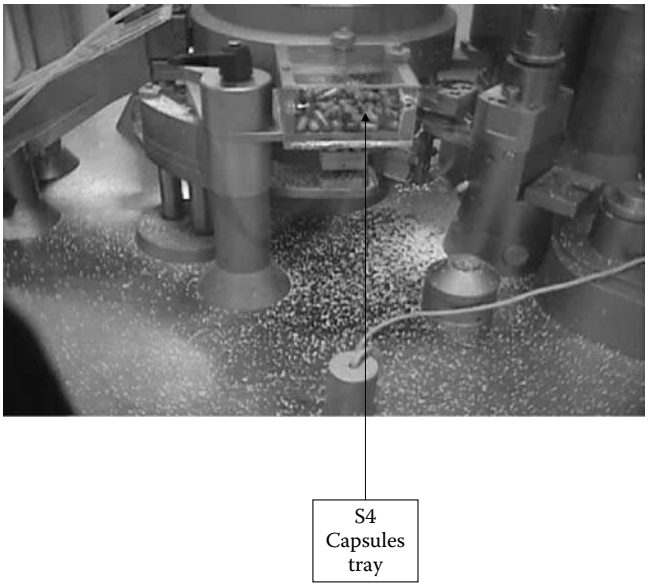


FIGURE 20.8.2.3
Capsule-filling machine tray.

Your Company's Logo **Your Company's Name**

Attachment IVd

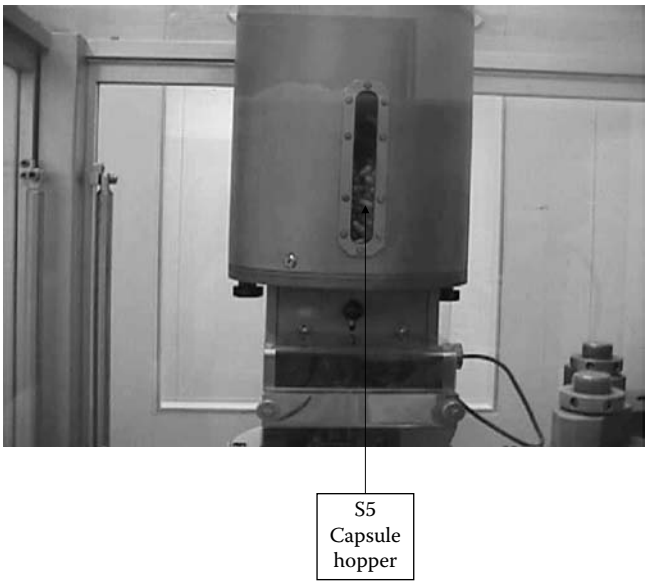


FIGURE 20.8.2.4
Capsules hopper.

Your Company's Logo **Your Company's Name**

Attachment IVe

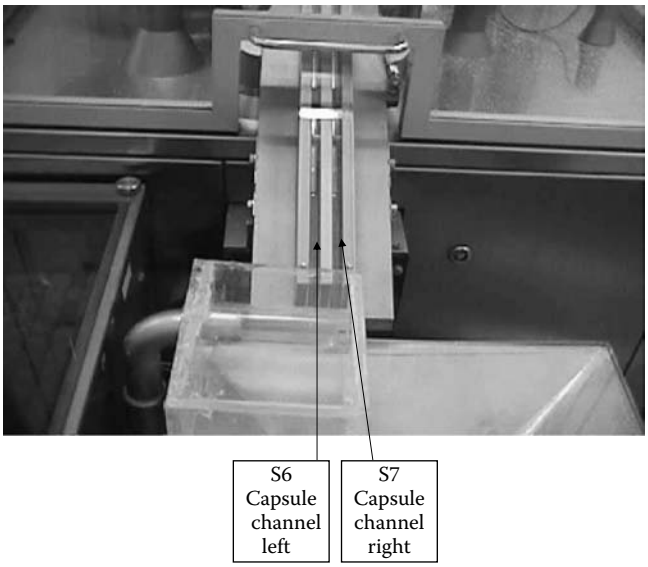


FIGURE 20.8.2.5
Capsules channels.

Your Company's Logo **Your Company's Name**

Attachment IVf

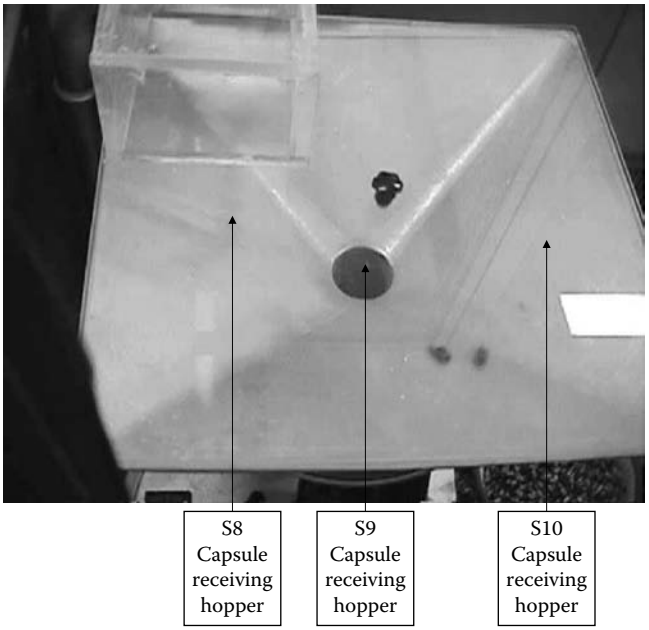


FIGURE 20.8.2.6
Capsules-receiving hopper.

Your Company's Logo **Your Company's Name**

Attachment IVg

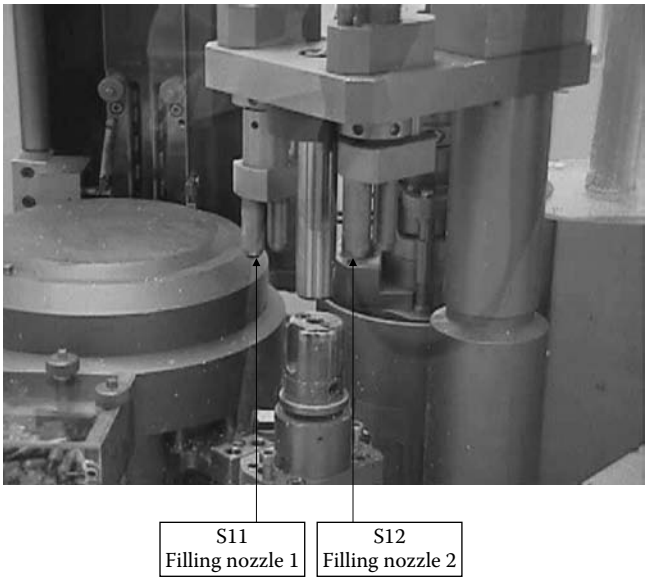


FIGURE 20.8.2.7
Capsules-filling nozzles.

Your Company's Logo **Your Company's Name**

Attachment IVh

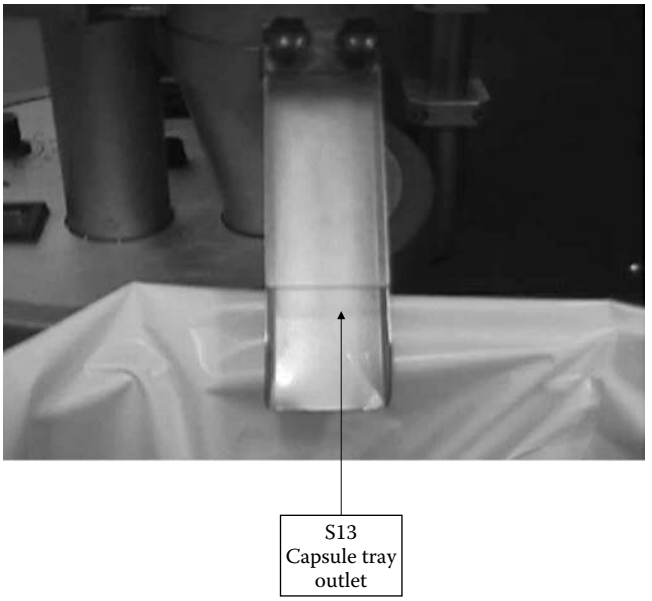


FIGURE 20.8.2.8
Capsules tray.

Your Company's Logo **Your Company's Name**

Attachment V

Calculation for Surface Swabs

Formula:

$$\text{MAC} = \frac{\text{TD} \times \text{BS} \times \text{SF}}{\text{LDD}},$$

where MAC is the maximum allowable carryover, TDis a single therapeutic dose, BS is the batch size of the next product to be manufactured in the same equipment, SF* is the safety factor (0.001), and LDD is the largest daily dose of the next product to be manufactured in the same equipment.

Calculation:

$$Y = X \times \text{surface area},$$

where Y is the active ingredient on the corresponding equipment part, X is the active ingredient recovered from 25 cm^2 by swab from the corresponding equipment part, and surface area is the area of corresponding equipment parts A–M.

$$Z = Y1 + Y2 + Y3 + Y4 + Y5 + Y6 + Y7 + Y8 + Y9 + Y10 + Y11 + Y12 + Y13,$$

where Z is the total active ingredient recovered from the machine, $Y1$ is the active ingredient recovered from part S1, $Y2$ is the active ingredient recovered from part S2, $Y3$ is the active ingredient recovered from part S3, $Y4$ is the active ingredient recovered from part S4, $Y5$ is the active ingredient recovered from part S5, $Y6$ is the active ingredient recovered from part S6, $Y7$ is the active ingredient recovered from part S7, $Y8$ is the active ingredient recovered from part S8, $Y9$ is the active ingredient recovered from part S9, $Y10$ is the active ingredient recovered from part S10, $Y11$ is the active ingredient recovered from part S11, $Y12$ is the active ingredient recovered from part S12, and $Y13$ is the active ingredient recovered from part S13.

Acceptance criteria:

$$Z \leq \text{MAC}.$$

* 1/100 to 1/1000 of a normal daily dose for oral products (PDA Guideline).

Your Company's Logo **Your Company's Name**

Attachment VI

Swab Analysis Results

Sampling Location	Sampling ID	Visual Inspection	Bio-Burden Test NMT 33 cfu/25 cm^2	Carryover HPLC Result per 25 cm^2 (*X*)	Carryover 25 cm^2 × Surface Area Total Carryover $Y = (X) \times (A–M)$
Pellet hopper	S1				
Machine base (right)	S2				
Machine base (left)	S3				
Capsules tray	S4				
Capsule hopper	S5				
Capsule channel (left)	S6				
Capsule channel (right)	S7				
Capsule receiving hopper location 1	S8				
Capsule receiving hopper location 2	S9				
Capsule receiving hopper location 3	S10				
Filling nozzle 1	S11				
Filling nozzle 2	S12				
Capsule tray	S13				

Performed by: _____ Date: _____

Checked by: _____ Date: _____

Your Company's Logo **Your Company's Name**

Attachment VII

Swab Sampling Recovery (Challenge) Test

Name of Active Material	Concentration of Standard Solution	Type of Swab	Total Area of Swab	% Recovery of Active Ingredient	% Recovery as per Limit NLT (70%)	
					Y	N

Your Company's Logo **Your Company's Name**

Attachment VIII

Training Record Verification (Production Staff)

The following staff found trained on cleaning of the equipment.

Using SOP No. ABC-6; Revision No.; Issued on; Date

Name: _____ ID No.: _____ Sign.: _____ Date: _____

Name: _____ ID No.: _____ Sign.: _____ Date: _____

Training Record Verification (Analyst)

The following analyst trained on STM No. _____

Name: _____ ID No.: _____ Sign.: _____ Date: _____

Verified by: _____ Checked by: _____

Training documentation copy attached.

CLV-20.9

Cleaning Validation Protocol for Film-Coating Pan

Your Company's Logo **Your Company's Name**

ABC Pharmaceutical Company	**CLEANING VALIDATION PROTOCOL** **Equipment Name**	
	Issued on **Date**	**Protocol Number** **CLVS-000**
	Location **Granulation Area** **Room No. 000**	

Equipment.....Film-Coating Pan

Model.....Cota

Manufacturer .....Company/Country

20.9.1 Objective

The objective of this protocol is to demonstrate that the cleaning procedure No. ABC-001 will successfully and consistently reduce the level of residues to a predetermined level of acceptability, so as to prevent contamination (product or cleaning process related) from adversely affecting the safety and quality of the next product manufactured.

20.9.2 Scope

This protocol will cover pre- and postcleaning of the film coating machine for the tablet products (Figure 20.9.1).

Your Company's Logo **Your Company's Name**

FIGURE 20.9.1
ABC cota film-coating machine (front view).

In the grouping matrix, products are divided into various groups based on their

a. Water solubility
b. Therapeutic dosage
c. Toxicity
d. Batch size (in kg)

From each group, one worst-case product is considered for cleaning validation (Table 20.9.1).

TABLE 20.9.1
Worst Case for the Film-Coating Pan

Products	Reason for Selecting as Worst Case
Ciprofloxacin F/C tablet 500 mg	Six ingredients insoluble in water
Cetralon 10 mg tablets	Therapeutic dosage (10.0 mg)
Diclofenac E/C tablet 50 mg	High toxicity level (LD_{50} 150 mg/kg oral rat)
Vitamin B tablets	Largest batch size (682 kg)

Your Company's Logo

Your Company's Name

20.9.3 Responsibility

The following personnel are responsible for the execution of this protocol:

QA officer/production officer/QA inspector/QC chemist/analyst/machine operator.

For details, please refer to Attachment II.

20.9.4 Description of the Cleaning Process

The film coating machine should be cleaned manually as per SOP No. ABC-001.

4.1 Label the machine "Under Cleaning"
4.2 Start the machine without starting the exhaust
4.3 Spray 20 L of 10% sodium bicarbonate in purified water solution or 5% sodium hydroxide solution in purified water to clean the machine after spraying eudragit
4.4 Spray 20 L of purified water to clean the hoses and spraying guns
4.5 Clean the inside of the machine and baffles with a brush and a sponge
4.6 Flush the inside of the machine and baffles with purified water by means of a hose
4.7 Dry the machine by applying hot air at 70–80°C for 15 min with the exhaust off
4.8 Spray the machine with 70% alcohol
4.9 Clean the door and outside of the machine with a wet clean towel
4.10 In the case of a different product, follow the same procedure of cleaning plus dismantling and cleaning the distributing arm
4.11 Clean the exhaust duct in washing area by flushing hot water every month
4.12 Run the machine for 20 min without heating to expel the residual alcohol of step 4.7
4.13 Label the machine "Clean"
4.14 Make entries in the equipment cleaning, maintenance, and production logbook as per SOP No. ABC-002

20.9.4.1 Difficult-to-Clean Parts

i. Arms
ii. Baffles
iii. Spraying guns

Your Company's Logo

Your Company's Name

20.9.5 Description of the Sampling Process

20.9.5.1 Sampling Technique

The surface swab sampling technique is used for the film coating machine (swabs with DIW/alcohol).

20.9.5.2 Sampling Precautions

Before taking the sample, wear

i. Gloves
ii. Face mask

20.9.5.3 Handling of Samples

i. After collecting, keep the swab samples for MAC in the refrigerator
ii. HPLC samples should be kept at room temperature for at least 2 h before testing starts

20.9.5.4 Surface Swabs

20.9.5.4.1 Procedure for Sampling

Samples for the internal surfaces are taken by moistening the swab (readymade sterile cotton swab) with a suitable solvent (DIW/alcohol–water–alcohol). Sample a 25-cm^2 area (see Figures 20.9.2 and 20.9.3) and place the swab in a test tube containing 10 mL of solvent (suitable solvent). Swab samples from each part of the film coating machine are collected as per Table 20.9.2.

TABLE 20.9.2

Surface Swabs Sampling Description

Description	Sample Location	Sample ID	Reference
ABC Cota	Pan surface	S1–S2	Figure 20.9.2
	Arm	S3	
	Spray	S4	
	Spray	S5	
	Tubing	S6	
Solution preparation	Wall center	S7	Figure 20.9.3
	Tubing	S8	
	Mixer rod	S9	
	Mixer blade	S10	
	Wall bottom	S11	

Your Company's Logo **Your Company's Name**

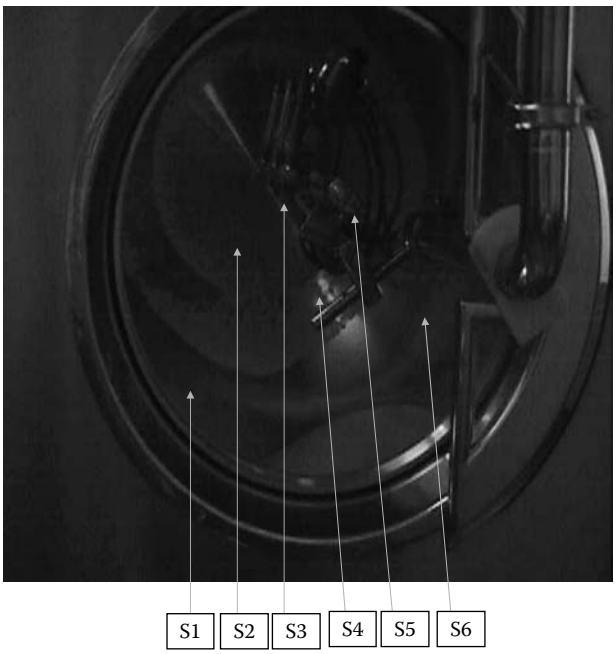


FIGURE 20.9.2
Pan surface, arm, and spray gun.

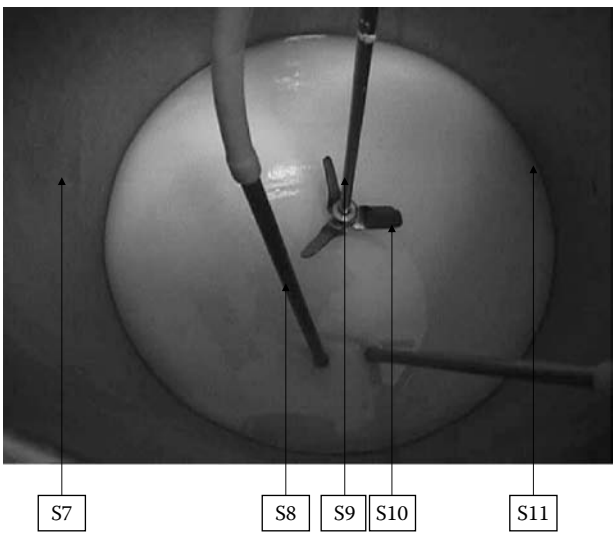


FIGURE 20.9.3
Solution preparation mixer rod, blade, and tubing.

Your Company's Logo **Your Company's Name**

20.9.6 Test Functions

a. *Visual inspection:* Inspection of the film coating machine is performed visually at the end of the cleaning procedure.

b. *Maximum allowable carryover:* The test for MAC of the swab is performed as per the HPLC method suitable for each product residue.

Notes:

- Analysis is carried out by pooling the 10 mL swab extraction for specific analysis.
- The validated HPLC test method is used for the determination of chemical residues.

c. *Bio-burden test:* The test for bio-burden is performed as per STM No. MC-0001 by the Microbiology section.

d. *Swab recovery challenge test:* The recovery challenge test is performed of the swab sample as per PDA *Journal of Pharmaceutical Science and Technology.*

20.9.7 Verification of Documents

i. Verify the film coating machine cleaning procedure.

ii. Verify the film coating machine cleaning logbook records.

iii. Verify the cleaning operators and analyst training record (refer to Attachment V).

20.9.8 Documentation

i. All analysis results are recorded in the analysis logbook.

ii. Printouts and chromatograms are attached to the validation report and a copy of that is also attached to the analytical logbook.

iii. A second analyst will verify all analyses and data.

iv. The cleaning validation officer will check all training records.

v. The final report for cleaning validation is prepared by the QA officer.

20.9.9 Acceptance Criteria

a. *Visual inspection:* The visible internal equipment surfaces and all critical and difficult-to-clean parts are optically free from residue, and the color of the final rinse water is comparable to DIW.

Your Company's Logo **Your Company's Name**

b. *Maximum allowable carryover:* The active ingredient calculated (Z) is either equal to or less than the MAC. Based on the "worst-case" concept,

$$Z \leq \text{MAC},$$

$$\text{MAC} = \frac{\text{TD} \times \text{BS} \times \text{SF}}{\text{LDD}},$$

where MAC is the maximum allowable carryover, TD is a single therapeutic dose, BS is the batch size of the next product to be manufactured in the same equipment, SF* is the safety factor (0.001), and LDD is the largest daily dose of the next product to be manufactured in the same equipment.

The calculated value is the maximum amount of active ingredient of the worst-case product that is allowed to be carried over to the next batch.

Calculation:

$$Y = X \times \text{surface area},$$

where Y is the active ingredient on the corresponding equipment part, X is the active ingredient recovered from 25 cm^2 by swab from the corresponding equipment part, and surface area is the area of corresponding equipment parts A–K.

$$Z = Y1 + Y2 + Y3 + Y4 + Y5 + Y6 + Y7 + Y8 + Y9 + Y10 + Y11,$$

where Z is the total active ingredient recovered from the machine, $Y1$ is the active ingredient recovered from part A, $Y2$ is the active ingredient recovered from part B, $Y3$ is the active ingredient recovered from part C, $Y4$ is the active ingredient recovered from part D, $Y5$ is the active ingredient recovered from part E, $Y6$ is the active ingredient recovered from part F, $Y7$ is the active ingredient recovered from part G, $Y8$ is the active ingredient recovered from part H, $Y9$ is the active ingredient recovered from part I, $Y10$ is the active ingredient recovered from part J, and $Y11$ is the active ingredient recovered from part K.

Acceptance criteria:

$$Z \leq \text{MAC}.$$

c. *Bio-burden:* The bio-burden should not be more than 33 cfu/25 cm^2 for the swabs.

d. *Swab recovery challenge test:* The swab recovery challenge test should be 70% of the known concentration of standard spiked.

* 1/100 to 1/1000 of a normal daily dose for oral products (PDA Guideline).

Your Company's Logo **Your Company's Name**

20.9.10 List of Attachments

Attachment I	Description of equipment and product
Attachment II	Cleaning/testing responsibilities
Attachment III	Sampling and testing plan
Attachment IV	Calculations for surface swabs
Attachment V	Training record verification
Attachment VI	Swabs analysis results
Attachment VII	Swab sampling recovery challenge test results

Your Company's Logo **Your Company's Name**

Attachment I

Description of Equipment and Product

Equipment Name: _____

Serial No.: _____

Capacity: _____

Room No.: _____

Product Name: _____

Worst-Case Products

- ☐ Ciprofloxacin F/C tablet 500 mg
- ☐ Diclofenac E/C tablet 50 mg
- ☐ Cetrizine 10 mg tablets
- ☐ Vitamin B tablets

Batch No. of the Product: _____

Next Product to Be Manufactured in the Same Equipment: _____

Manufacturing Date: _____

Active Ingredient: _____

Therapeutic Group: _____

Cleaning Date: _____

Cleaning SOP No.: _____ Revision No.: _____

Sampling Technique: _____

Cleaning Sample Analysis Date/Time: _____ Result: _____

Test Method Reference: _____ Reference Analytical Logbook: _____

Limit of Detection: _____

Safety Factor: _____

Your Company's Logo **Your Company's Name**

Attachment II

Worst-Case Products

- ☐ Ciprofloxacin F/C tablet 500 mg
- ☐ Diclofenac E/C tablet 50 mg
- ☐ Cetrizine 10 mg tablets
- ☐ Vitamin B tablets

Cleaning/Testing Responsibilities

Cleaning/Testing	Done by	Recorded on	Checked by
Equipment cleaning	Machine operator	Equipment usage/ cleaning logbook	Production supervisor
Visual inspection	Validation officer	Analytical logbook	—
Swab sample	Machine operator/ validation officer	Sampling sheet	—
MAC	Validation officer/QC analyst	Analytical logbook	QC officer
Bio-burden	Microbiologist	Analytical logbook	QC assistant manager, microbiology
Swab recovery challenge test	Analyst	Analytical logbook	Senior analyst

Your Company's Logo **Your Company's Name**

Attachment III

Worst-Case Products

- ☐ Ciprofloxacin F/C tablet 500 mg
- ☐ Diclofenac E/C tablet 50 mg
- ☐ Cetrizine 10 mg tablets
- ☐ Vitamin B tablets

Sampling and Testing Plan

S. No.	Visual Inspection	Detergent Detection	Identification Labeling	Sample Area (cm^2)	Surface Area in Contact with Product (cm^2)	MAC	Less Than or Equal to Limit of Detection	Bio-Burden NMT 33 cfu/ 25 cm^2	Testing Method
1			S1	25	16,000				STM-MC-001
2			S2	25	16,000				
3			S3	25	200				
4			S4	25	2100				
5			S5	25	2100				
6			S6	25	150				
7			S7	25	300				
8			S8	25	50				
9			S9	25	50				
10			S10	25	70				
11			S11	25	150				

Your Company's Logo **Your Company's Name**

Attachment IV

Worst-Case Products

- ☐ Ciprofloxacin F/C tablet 500 mg
- ☐ Diclofenac E/C tablet 50 mg
- ☐ Cetrizine 10 mg tablets
- ☐ Vitamin B tablets

Calculation for Surface Swabs

$$\text{MAC} = \frac{\text{TD} \times \text{BS} \times \text{SF}}{\text{LDD}}$$

Calculation:

$$Y = X \times \text{surface area},$$

where Y is the active ingredient on the corresponding equipment part, X is the active ingredient recovered from 25 cm^2 by swab from the corresponding equipment part, and surface area is the area of corresponding equipment parts A–E.

$$Z = Y1 + Y2 + Y3 + Y4 + Y5 + Y6 + Y7 + Y8 + Y9 + Y10 + Y11,$$

where Z is the total active ingredient recovered from the machine, $Y1$ is the active ingredient recovered from part S1, $Y2$ is the active ingredient recovered from part S2, $Y3$ is the active ingredient recovered from part S3, $Y4$ is the active ingredient recovered from part S4, $Y5$ is the active ingredient recovered from part S5, $Y6$ is the active ingredient recovered from part S6, $Y7$ is the active ingredient recovered from part S7, $Y8$ is the active ingredient recovered from part S8, $Y9$ is the active ingredient recovered from part S9, $Y10$ is the active ingredient recovered from part S10, and $Y11$ is the active ingredient recovered from part S11.

Acceptance criteria:

$$Z \leq \text{MAC}.$$

Your Company's Logo **Your Company's Name**

Attachment V

Worst-Case Products

- ☐ Ciprofloxacin F/C tablet 500 mg
- ☐ Diclofenac E/C tablet 50 mg
- ☐ Cetrizine 10 mg tablets
- ☐ Vitamin B tablets

Training Record Verification (Production Staff)

The following staff found trained on cleaning of the equipment.

Using SOP No. ABC-006; Revision No; Issued on; Date

Name: _____ ID No.: _____ Sign.: _____ Date: _____

Name: _____ ID No.: _____ Sign.: _____ Date: _____

Training Record Verification (Analyst)

The following analyst trained on STM No.: _____

Name: _____ ID No.: _____ Sign.: _____ Date: _____

Performed by: _____ Checked by: _____

Date: _____ Date: _____

Your Company's Logo **Your Company's Name**

Attachment VI

Worst-Case Products

- ☐ Ciprofloxacin F/C tablet 500 mg
- ☐ Diclofenac E/C tablet 50 mg
- ☐ Cetrizine 10 mg tablets
- ☐ Vitamin B tablets

Swab Analysis Results

Sampling Location	Visual Inspection	Bio-Burden Test NMT 33 cfu/ 25 cm^2 swab	Carryover HPLC Result per 25 cm^2 (X)	Carryover 25 cm^2 × Surface Area Total Carryover $Y = X \times (A–R)$
S1				
S2				
S3				
S4				
S5				
S6				
S7				
S8				
S9				
S10				
S11				

Your Company's Logo **Your Company's Name**

Attachment VII

Swab Sampling Recovery (Challenge) Test

Name of Active Material	Concentration of Standard Solution	Type of Swab	Total Area of Swab	% Recovery of Active Ingredient	% Recovery as per Limit NLT (70%)	
					Y	N

CLV-20.10

Cleaning Validation Protocol for Sugar-Coating Pan

Your Company's Logo **Your Company's Name**

ABC Pharmaceutical Company	**CLEANING VALIDATION PROTOCOL** **Equipment Name**	
	Issued on **Date**	**Protocol Number** **CLVS-000**
	Location **Coating Area** **Room No. 000**	

Equipment.....**Sugar-Coating Pan**

Model.....**XX kg**

Manufacturer.....**Company, Country**

20.10.1 Objective

The objective of this protocol is to demonstrate that the cleaning procedure No. ABC-001 will successfully and consistently reduce the level of residues to a predetermined level of acceptability, so as to prevent contamination (product or cleaning process related) from adversely affecting the safety and quality of the next product manufactured.

20.10.2 Scope

This protocol will cover cleaning of the sugar-coating pan of the tablets products.
In the grouping matrix, products are divided into various groups based on their

a. Water solubility
b. Therapeutic dosage

Your Company's Logo **Your Company's Name**

c. Toxicity
d. Batch size (quantity of active used)

From each group, one worst-case product is considered for cleaning validation (Table 20.10.1).

20.10.3 Responsibility

The following personnel are responsible for the execution of this protocol:

Validation officer/production officer/QA inspector/QC chemist/analyst/machine operator.

For details, please refer to Attachment II.

20.10.4 Description of the Cleaning Process

Sugar-coating pan is cleaned manually as per SOP No. ABC-001.

4.1 Remove the arm from the coating pan and send it to the washing room.
4.2 Clean the arm with DIW in the washing room.
4.3 Charge 30 L of DIW inside the coating pan.
4.4 Operate the pan for 30 min.
4.5 Discharge the water outside the coating pan by means of a vacuum pump or manually.

TABLE 20.10.1

Sugar-Coated Worst Products

Products	Reason for Selecting as Worst Case
Sennoside 12 mg tablet	Three ingredients insoluble in water are as follows:
	Avicel (7)
	Magnesium stearate (7)
	Aerosil 200 (7)
Bisacodyl 5 mg.	Minimum therapeutic dose (5 mg)
Ibuprofen 200 mg	Toxicity. LD_{50} 636 mg/kg oral rat
Ibuprofen 200 mg	Largest batch size (495 kg)

Your Company's Logo **Your Company's Name**

4.6 Charge 10 L of 95% alcohol outside the coating pan.
4.7 Operate the pan for 30 min.
4.8 Use a brush to remove the residues remaining inside the surface of the coating pan.
4.9 Discharge the alcohol outside the coating pan by means of a vacuum pump or manually.
4.10 Charge 25 L of DIW inside the pan.
4.11 Operate the coating pan for 10 min.
4.12 Discharge the water outside the coating pan.
4.13 Apply 80°C hot air to dry the coating pan for 15 min.
4.14 Repeat steps 4.10, 4.11, and 4.12 if required.
4.15 Clean the outside of coating pan and panel with a clean towel wetted with 1% liquid soap, followed by a wet clean towel.
4.16 Label the equipment "CLEAN".
4.17 Ask the production supervisor to check the cleanliness.
4.18 Make entries in the equipment cleaning, maintenance, and production usage record as per SOP No. ABC-002.

20.10.4.1 Difficult-to-Clean Parts

i. Suspension coater
ii. Arms

20.10.5 Description of the Sampling Process

20.10.5.1 Sampling Technique

The swab sampling technique is used to take the sample from the sugar cota pan.

Sampling Precautions

For sampling, wear the following:

i. Gloves
ii. Face mask

20.10.5.2 Handling of Samples

i. HPLC analysis should be completed within 24 h of collection.
ii. HPLC samples should be kept at room temperature for at least 2 h before testing.

Your Company's Logo

Your Company's Name

20.10.5.3 Surface Swabs

20.10.5.3.1 Procedure for Sampling

Samples of the internal surfaces are taken by moistening the swab (ready-made sterile cotton swab) with a suitable solvent (DIW/alcohol–water–alcohol). Sample a 25-cm^2 area (see Figures 20.10.1 through 20.10.3) and place the swab in a test tube containing 10 mL of solvent (suitable solvent). Swab samples from each part of the sugar-coating pan are collected as per Table 20.10.2.

TABLE 20.10.2

Surface Swabs Sampling Description

Description	Sample Location	Sample ID	Reference
Sugar-coating pan	Pan surface left	S1	Figure 20.10.1
	Pan surface center	S2	
	Pan surface right	S3	
	Arm	S4	Figure 20.10.2
	Arm	S5	Figure 20.10.3
	Suspension coater	S6	
	Solution tank wall surface	S7	
	Solution tank wall surface pipe	S8	
	Solution tank wall surface	S9	

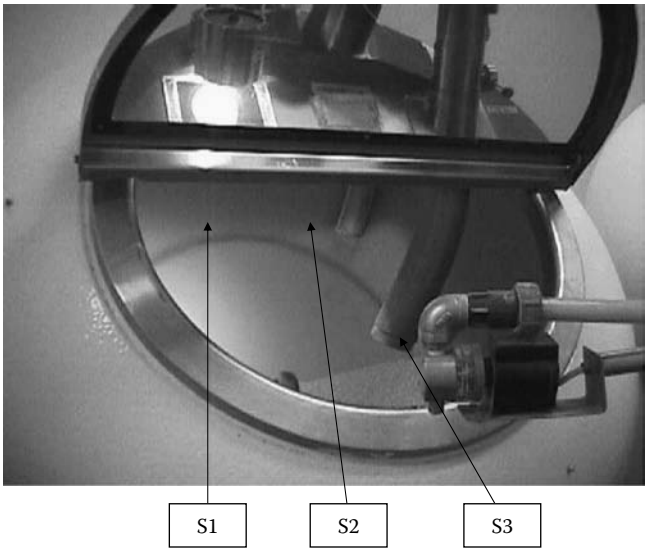


FIGURE 20.10.1
Sugar-coating pan.

Your Company's Logo **Your Company's Name**

FIGURE 20.10.2
Coating pan arm.

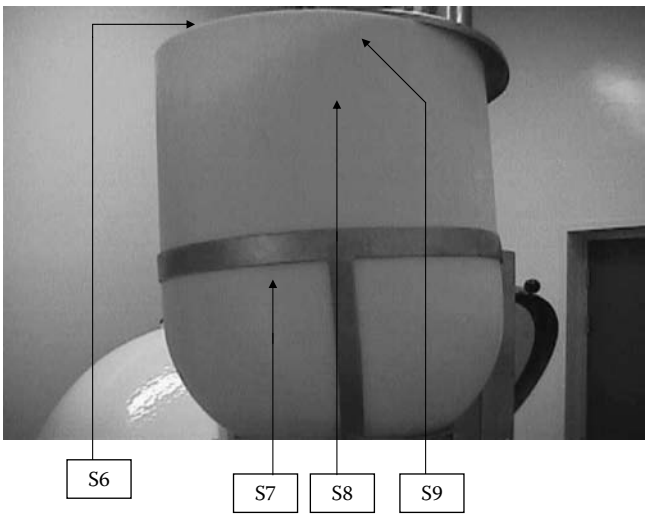


FIGURE 20.10.3
Solution preparation wall surface and pipe.

Your Company's Logo

Your Company's Name

20.10.6 Test Functions

a. *Visual inspection:* Visual inspection of sugar-coating pan is performed as per SOP No. ABC-003. Sampling procedure for cleaning validation

b. *Maximum allowable carryover:* The test for MAC of the final rinse/swab is performed as per the HPLC method suitable for each product residue.

Notes:

- Analysis will be carried out by pooling the 10 mL swab extraction for specific analysis.
- The validated HPLC test method is used for the determination of chemical residues.

c. *Bio-burden test:* The test for bio-burden is performed as per STM No. MC-001 by the QC Microbiology section.

d. *Swab recovery challenge test:* The recovery challenge test of the swab sample is performed as per PDA *Journal of Pharmaceutical Science and Technology.*

20.10.7 Verification of Documents

i. Verify the sugar-coating pan cleaning procedure.
ii. Verify the sugar-coating pan cleaning logbook records.
iii. Verify the cleaning operators and analyst training record (refer to Attachment V).

20.10.8 Documentation

i. All analysis results are recorded in the analysis logbook.
ii. Printouts and chromatograms are attached to the validation report and a copy of that is also attached to the analytical logbook.
iii. A second analyst will verify all analyses and data.
iv. The QA officer will check all training records.
v. The final report for cleaning validation is prepared by the QA officer.

Your Company's Logo

Your Company's Name

20.10.9 Acceptance Criteria

a. *Visual inspection:* The visible internal equipment surfaces and all critical and difficult-to-clean parts are optically free from residue and the color of the final rinse water is comparable to DIW.

b. *Maximum allowable carryover:* The active ingredient calculated (*Z*) is either equal to or less than the MAC.

$$Z \leq \text{MAC},$$

$$\text{MAC} = \frac{\text{TD} \times \text{BS} \times \text{SF}}{\text{LDD}},$$

where MAC is the maximum allowable carryover, TD is a single therapeutic dose, BS is the batch size of the next product to be manufactured in the same equipment, SF* is the safety factor (0.001), and LDD is the largest daily dose of the next product to be manufactured in the same equipment.

The calculated value is the maximum amount of active ingredient of worst-case product that is allowed to be carried over to the next batch.

Calculation:

$$Y = X \times \text{surface area}$$

where *Y* is the active ingredient on the corresponding equipment part, *X* is the active ingredient recovered from 25 cm^2 by swab from the corresponding equipment part, and surface area is the area of corresponding equipment parts A–I.

$$Z = Y1 + Y2 + Y3 + Y4 + Y5 + Y6 + Y7 + Y8 + Y9,$$

where *Z* is the total active ingredient recovered from the machine, *Y*1 is the active ingredient recovered from part S1, *Y*2 is the active ingredient recovered from part S2, *Y*3 is the active ingredient recovered from part S3, *Y*4 is the active ingredient recovered from part S4, *Y*5 is the active ingredient recovered from part S5, *Y*6 is the active ingredient recovered from part S6, *Y*7 is the active ingredient recovered from part S7, *Y*8 is the active ingredient recovered from part S8, and *Y*9 is the active ingredient recovered from part S9.

Acceptance criteria:

$$Z \leq \text{MAC}.$$

c. *Bio-burden:* The bio-burden should not be more than 33 cfu/25 cm^2 for the swabs.

d. *Swab recovery challenge test:* The swab recovery challenge test should be 70% of the known concentration of standard spiked.

* 1/100 to 1/1000 of a normal daily dose for oral products (PDA Guideline).

Your Company's Logo **Your Company's Name**

20.10.10 List of Attachments

Attachment I	Description of equipment and product
Attachment II	Cleaning/testing responsibilities
Attachment III	Sampling and testing plan.
Attachment IV	Calculations for surface swabs.
Attachment V	Training record verification
Attachment VI	Swabs analysis results
Attachment VII	Swab sampling recovery challenge test results

Your Company's Logo **Your Company's Name**

Attachment I

Description of Equipment and Product

Equipment Name: _____

Serial No.: _____

Capacity: _____

Location: _____

Room No.: _____

Product Name: _____

Batch No. of the Product: _____

Worst-Case Products

- ☐ Sennoside 12 mg
- ☐ Bisacodyl 5 mg
- ☐ Ibuprofen 200 mg

Next Product to Be Manufactured in the Same Equipment: _____

Manufacturing Date: _____

Active Ingredient: _____

Therapeutic Group: _____

Cleaning Date: _____

Cleaning SOP No. _____ Revision No. _____

Sampling Technique: _____ Test Method Reference: _____

Cleaning Sample Analysis Date/Time: _____ Result: _____

Limit of Detection: _____ Reference Analytical Logbook: _____

Safety Factor: _____

Your Company's Logo **Your Company's Name**

Attachment II

Worst-Case Products

- ☐ Sennoside 12 mg
- ☐ Bisacodyl 5 mg
- ☐ Ibuprofen 200 mg

Cleaning/Testing Responsibilities

Cleaning/Testing	Done by	Recorded on	Checked by
Equipment cleaning	Machine operator	Equipment usage/ cleaning logbook	Production supervisor
Visual inspection	Validation officer	Analytical logbook	—
Swab sample	Machine operator/ validation officer	Sampling sheet	—
MAC	Validation officer/QC analyst	Analytical logbook	QC analyst
Bio-burden	Microbiologist	Analytical logbook	Manager QC, microbiology
Swab recovery challenge test	Analyst	Analytical logbook	Senior analyst

Your Company's Logo **Your Company's Name**

Attachment III

Worst-Case Products

☐ Sennoside 12 mg

☐ Bisacodyl 5 mg

☐ Ibuprofen 200 mg

Sampling and Testing Plan

S. No.	Visual Inspection	Identification Labeling	Sample Area (cm^2)	Surface Area (cm^2)	MAC	Less Than or Equal to the Limit of Detection	Bio-Burden NMT 33 cfu/ swab	Testing Method
1		S1	25	12,560				STM-MC-001
2		S2	25	12,560				
3		S3	25	12,560				
4		S4	25	350				
5		S5	25	350				
6		S6	25	8950				
7		S7	25	5950				
8		S8	25	5950				
9		S9	25	5950				

Your Company's Logo **Your Company's Name**

Attachment IV

Worst-Case Products

- ☐ Sennoside 12 mg
- ☐ Bisacodyl 5 mg
- ☐ Ibuprofen 200 mg

Calculation for Surface Swabs

$$\frac{\text{MAC} = \text{TD} \times \text{BS} \times \text{SF}}{\text{LDD}}$$

Calculation:

$$Y = X \times \text{surface area},$$

where Y is the active ingredient on the corresponding equipment part, X is the active ingredient recovered from 25 cm^2 by swab from the corresponding equipment part, and surface area is the area of corresponding equipment parts A–I.

$$Z = Y1 + Y2 + Y3 + Y4 + Y5 + Y6 + Y7 + Y8 + Y9,$$

where Z is the total active ingredient recovered from the machine, $Y1$ is the active ingredient recovered from part S1, $Y2$ is the active ingredient recovered from part S2, $Y3$ is the active ingredient recovered from part S3, $Y4$ is the active ingredient recovered from part S4, $Y5$ is the active ingredient recovered from part S5, $Y6$ is the active ingredient recovered from part S6, $Y7$ is the active ingredient recovered from part S7, $Y8$ is the active ingredient recovered from part S8, and $Y9$ is the active ingredient recovered from part S9.

Acceptance criteria:

$$Z \leq \text{MAC}.$$

Your Company's Logo **Your Company's Name**

Attachment V

Worst-Case Products

- ☐ Sennoside 12 mg
- ☐ Bisacodyl 5 mg
- ☐ Ibuprofen 200 mg

Training Record Verification (Production Staff)

Following staff found trained on cleaning of equipment.

Using SOP No. ABC-004; Revision No., Issued on: Date

Name:_____ ID No.:_____ Sign.:_____ Date:_____

Name:_____ ID No.:_____ Sign.:_____ Date:_____

Training Record Verification (Analyst)

Following analyst trained on STM No._____

Name:_____ ID No.:_____ Sign.:_____ Date:_____

Performed by: _____ Date: _____

Checked by: _____ Date: _____

Your Company's Logo **Your Company's Name**

Attachment VI

Worst-Case Products

- ☐ Sennoside 12 mg
- ☐ Bisacodyl 5 mg
- ☐ Ibuprofen 200 mg

Swab Analysis Results

Sampling Location	Visual Inspection	Bio-Burden Test NMT 33 cfu/mL	Carryover HPLC Result per 25 cm^2 (X)	Carryover 25 cm^2 × Surface Area Total Carryover $Y = X \times (A - S)$
S1				
S2				
S3				
S4				
S5				
S6				
S7				
S8				
S9				

Your Company's Logo **Your Company's Name**

Attachment VII

Worst-Case Products

- ☐ Sennoside 12 mg
- ☐ Bisacodyl 5 mg
- ☐ Ibuprofen 200 mg

Swab Sampling Recovery (Challenge) Test

Name of Active Material	Concentration of Standard Solution	Type of Swab	Total Area of Swab	% Recovery of Active Ingredient	% Recovery as per Limit (70%)	
					Y	N

CLV-21

Cleaning Validation Product Grouping Matrix (Syrup)

Your Company's Logo

Your Company's Name

Product	Ingredients	Batch Size (L)	Maximum Usage per Day	Toxicity Level LD_{50}	Solubility
Paracetamol	Paracetamol	7500	4 g	2404 mg/kg oral rat	3
Diphenhydramine	Diphenhydramine HCl	7500	162 mg	500 mg/kg oral rat	1
Salbutamol	Salbutamol sulfate	7500	16 mg	660 mg/kg oral rat	1
B complex	Vitamin B_1, B_2, B_6, and B_{12}	7500	45 mg	10,000 mg/kg oral rat	4
Ephedrine	Ephedrine HCl	7500	60 mg	710 mg/kg oral rat	1
	Chlorpheniramine maleate		8 mg	188 mg/kg oral rat	2
Chlorpheniramine maleate	Chlorpheniramine maleate	7500	12 mg	3000 mg/kg oral rat	2
Antiflu	Paracetamol	7500	360 mg	1000 mg/kg oral rat	3
	Pseudoephedrine HCl		120 mg	1000 mg/kg oral rat	1
	Chlorpheniramine maleate			520 mg/kg oral rat	2
Promethazine	Promethazine HCl	7500	50 mg	255 mg/kg oral rat	1
Pheniramine	Pheniramine maleate	7500	30 mg	300 mg/kg oral rat	1
Vitamins A and B complex	Vitamin A	7500	5000 IU	7910 mg/kg oral rat	7
	B_2		2 mg	>20,000 mg/kg oral rat	3
	B_1		5 mg	>10,000 mg/kg oral rat	2
	B_6		6 mg	10,000 mg/kg oral rat	2
	B_{12}		6 mcg	>8000	4
	Nicotinamide		20 mg	3500 mg/kg oral rat	2
	Vitamin D		500 IU	2000 mg/kg oral rat	7
Valproate	Sodium valproate	7500	600 mg	670 mg/kg oral rat	1
Furosemide	Furosemide	7500	40 mg	2600 mg/kg oral rat	4
Bromhexine	Bromhexine HCl	7500	48 mg	1226 mg/kg oral rat	6
Clobutinol	Clobutinol HCl	7500	40 mg/day	802 mg/kg oral rat	2
	Orciprenaline sulfate			5538 mg/kg oral rat	2
Metoclopramide	Metoclopramide	7500	30 mg/day	280 mg/kg oral rat	1
Chlorpheniramine	Glyceryl guaiacolate	7500	6.0 mg/day	3000 mg/kg oral rat	3
	Chlorpheniramine				2

continued

Your Company's Logo **Your Company's Name**

Product	Ingredients	Batch Size (L)	Maximum Usage per Day	Toxicity Level LD_{50}	Solubility
Triprolidine	Triprolidine HCl	7500	3.75 mg	1000 mg/kg oral rat	3
	Pseudoephedrine HCl		90 mg		1
Dextro	Pseudoephedrine HCl		90 mg	1000 mg/kg oral rat	
	Dextromethorphan		30 mg	350 mg/kg oral rat	
Pseudoephedrine	Pseudoephedrine HCl	7500	90 mg	1000 mg/kg oral rat	3
Hyoscine	Hyoscine-*N*-butyl bromide	7500	50 mg	1040 mg/kg oral rat	2
Ketotifen	Ketotifen fumarate	7500	2 mg	360 mg/kg oral rat	5
Cetirizine	Cetirizine HCl	7500	5 mg		2
Iron	Ferrous sulfate	7500	800 mg	1520 mg/kg oral rat	2
Loratadine	Loratadine	7500	10 mg	Nontoxic	3
Ambroxol	Ambroxol HCl	7500	80 mg		4
Furosemide	Furosemide	7500	40 mg	2600 mg/kg oral rat	4
Multivitamins	Vitamin A	7500	5000 IU	7910 mg/kg oral rat	7
	Vitamin D		500 IU	2000 mg/kg oral rat	7
	Vitamin E		0.528 mg	10,000 mg/kg oral rat	7
	B_1		5 mg	>10,000 mg/kg oral rat	2
	B_6		6 mg	4000 mg/kg oral rat	2
	Nicotinamide		20 mg	3500 mg/kg oral rat	2
	B_2		2 mg	>20,000 mg/kg oral rat	3
Theophylline	Theophylline	2500	600 mg/day	666 mg/kg oral rat	2
Oxybuprocaine solution	Oxybuprocaine HCl chloride	7500			1
	Cetylpyridinium				1
	Tyrothricin				
Chlorhexidine mouthwash	Chlorhexidine	7500		7000 mg/kg oral rat	6

CLV-22

Cleaning Validation Product/Equipment Train (Syrup)

Your Company's Logo

Your Company's Name

Product	Equipments
Paracetamol	Manufacturing tank, holding tank, SS bins, mixer, online filtration, filling line 1/2/3
Diphenhydramine	Manufacturing tank, holding tank, SS bins A, SS bins B, mixer, vessel 300, online filtration, filling line 1/2/3
Salbutamol	Manufacturing tank, holding tank, SS bins A, SS bins B, mixer, vessel 300, online filtration, filling line 1/2/3
B complex	Manufacturing tank, holding tank, SS bins A, SS bins B, mixer, vessel 300, online filtration, filling line 1/2/3
Ephedrine/chlorpheniramine	Manufacturing tank, holding tank, SS bins A, SS bins B, mixer, vessel 300, online filtration, filling line 1/2/3
Chlorpheniramine	Manufacturing tank, holding tank, SS bins A, SS bins B, mixer, vessel 300, online filtration, filling line 1/2/3
Antiflu	Manufacturing tank, holding tank, SS bins A, SS bins B, mixer, vessel 300, online filtration, filling line 1/2/3
Promethasone	Manufacturing tank, holding tank, SS bins A, SS bins B, mixer, vessel 300, online filtration, filling line 1/2/3
Pheniramine	Manufacturing tank, holding tank, SS bins A, SS bins B, mixer, vessel 300, online filtration, filling line 1/2/3
Multivitamins	Manufacturing tank, holding tank, SS bins A, SS bins B, online filtration 20 µ, filling line 1/2/3
Sodium valproate	Manufacturing tank, holding tank, SS bins A, SS bins B, mixer, online filtration, filling line 1/2/3
Furosemide	Manufacturing tank, holding tank, SS bins A, SS bins B, mixer, online filtration, filling line 1/2/3
Bromhexine	Manufacturing tank, holding tank, SS bins A, SS bins B, mixer, online filtration, filling line 1/2/3
Orciprenaline/clobutinol	Manufacturing tank, holding tank, SS bins A, SS bins B, mixer, online filtration, filling line 1/2/3
Metoclopramide	Manufacturing tank, holding tank, SS bins A, SS bins B, mixer, online filtration, filling line 1/2/3
Chlorpheniramine/glyceryl guaiacolate	Manufacturing tank,holding tank, SS bins A, SS bins B, mixer, vessel 300, online filtration, filling line 1/2/3
Pseudoephedrine/triprolidine	Manufacturing tank, holding tank, SS bins A, SS bins B, mixer, vessel 300, online filtration, filling line 1/2/3

continued

Your Company's Logo **Your Company's Name**

Product	Equipments
Pseudoephedrine/dextromethorphan	Manufacturing tank, holding tank, SS bins A, SS bins B, mixer, vessel 300, online filtration, filling line 1/2/3
Pseudoephedrine	Manufacturing tank, holding tank, SS bins A, SS bins B, mixer, vessel 300, online filtration, filling line 1/2/3
Hyoscine-*N*–butyl bromide	Manufacturing tank, holding tank, SS bins A, SS bins B, mixer, online filtration, filling line 1/2/3
Ketotifen fumarate	Manufacturing tank, holding tank, SS bins A, SS bins B, mixer, online filtration, filling line 1/2/3
Cetirizine	Manufacturing tank, holding tank, SS bins A, SS bins B, mixer, online filtration, filling line 1/2/3
Ferrous sulfate	Manufacturing tank, holding tank, SS bins A, SS bins B, mixer, online filtration, filling line 1/2/3
Loratadine	Manufacturing tank, holding tank, SS bins A, SS bins B, mixer, online filtration, filling line 1/2/3
Ambroxol	Manufacturing tank, holding tank, SS bins A, SS bins B, mixer, online filtration, filling line 1/2/3
Vitamins	Manufacturing tank, holding tank, SS bins A, SS bins B, mixer, online filtration 650 µ, filling line 1/2/3
Theophylline	Manufacturing tank, holding tank, SS bins A, SS bins B, mixer, online filtration 650 µ, filling line 1/2/3
Oxybuprocaine solution	Manufacturing tank, holding tank, SS bins A, SS bins B, mixer, online filtration 650 µ, filling line 1/2/3
Chlorhexidine mouthwash	Manufacturing tank, holding tank, SS ZL bins, SS ZP bins, mixer, online filtration 20 µ, filling line 1/2/3

CLV-23

Worst-Case Products (Syrup)

Your Company's Logo

Your Company's Name

For manufacturing tanks MF-02, MF-03, and MF-04; holding tank numbers 1, 2, 3, 4, 5, and 6; and filling line numbers 1, 2, and 3

Products	Justification for Worst Case
Multivitamins	Less solubility (7), least soluble (vitamins A, D, and E)
Promethazone	High toxicity level (LD_{50} 255 mg/kg oral rat)
Paracetamol	Maximum daily dosage (4.0 g/day)

CLV-24

Cleaning Validation Product Grouping Matrix (Suspension)

Your Company's Logo

Your Company's Name

Product	Ingredients	Batch Size (L)	Maximum Usage per Day	Toxicity Level LD_{50}	Solubility
Kaolin	Kaolin light	7500	5.4 g		7
	Glycerol				5
	Pectin			20,000 mg/kg oral rat	2
	Propylene glycol			12,600 mg/kg oral rat	4
Al hydroxide	Al hydroxide	7500	720 mg	9500 mg/kg oral rat	7
	Mg hydroxide			Nontoxic	7
Cotrimoxazole	Cotrimoxazole	7500	360 mg		6
	Sulfamethoxazole			6200 mg/kg oral rat	7
Al–Magnesium	Magnesium	7500	1200 mg 120 mg	Nontoxic	7
	Aluminum silicate				7
	Simethicone			>2000 mg/kg oral rat	
Ibuprofen	Ibuprofen	7500	800 mg	636 mg/kg oral rat	7
Paracetamol	Paracetamol	7500	1000 mg	2404 mg/kg oral rat	3
Carbamazepine	Carbamazepine	7500	100 mg	1957 mg/kg oral rat	6
Al hydroxide plus	Al hydroxide	7500	720 mg	9500 mg/kg oral rat	7
	Mg hydroxide			8500 mg/kg oral rat	7
	Simethicone			Nontoxic	7
Al hydroxide II	Al hydroxide	7500	720 mg	950 mg/kg oral rat	7
	Mg hydroxide			8500 mg/kg oral rat	7
Metronidazole 125 mg	Metronidazole	7500	2150 mg	3000 mg/kg oral rat	4
Sucralfate	Sucralfate	7500	4 g	12,000 mg/kg oral rat	7
Mebendazole	Mebendazole	7500	100 mg	714 mg/kg oral rat	7
	Propylene glycol			20,000 mg/kg oral rat	7
Nystatin topical	Nystatin topical	7500	100,000 IU/1 mL	10,000 mg/kg oral rat	7
Terfenadine	Terfenadine	1000	120 mg	5 g/kg oral rat	
Attapulgite	Activated attapulgite	2500	5.4 g	Nontoxic	1
Albendazole	Albendazole	1000	400 mg	2400 mg/kg oral rat	7

CLV-25

Product Grouping/Equipment Train Matrix (Suspension)

Your Company's Logo

Your Company's Name

Product	Equipments
Kaolin	Manufacturing tank 5/6, holding tank 7/8/9, SS bins A, SS bins B, vessel 300, online filtration, filling line 4
Al–Mg hydroxide	Manufacturing tank 5/6, holding tank 7/8/9, SS bins A, SS bins B, vessel 300, online filtration, filling line 4
Cotrimoxazole	Manufacturing tank 5/6, holding tank 7/8/9, SS bins A, SS bins B, mixer, vessel 300, online filtration, sieve 630 µ, filling line 4
Simethicone	Manufacturing tank 5/6, holding tank 7/8/9, SS bins A, SS bins B, mixer, vessel 300, online filtration, sieve 630 µ, filling line 4
Ibuprofen	Manufacturing tank 5/6, holding tank 7/8/9, SS bins A, SS bins B, mixer, vessel 300, online filtration, sieve 500 µ, filling line 4
Paracetamol	Manufacturing tank 5/6, holding tank 7/8/9, SS bins A, SS bins B, mixer, online filtration, sieve 630 µ, filling line 4
Carbamazepine	Manufacturing tank 5/6, holding tank 7/8/9, SS bins A, SS bins B, mixer, vessel 300, online filtration, sieve 630 µ, filling line 4
Al–Mg hydroxide/simethicone	Manufacturing tank 5/6, holding tank 7/8/9, SS bins A, SS bins B, mixer, vessel 300, online filtration, filling line 4
Al–Mg hydroxide II	Manufacturing tank 5/6, holding tank 7/8/9, SS bins A, SS bins B, mixer, vessel 300, online filtration, filling line 4
Metronidazole 125 mg	Manufacturing tank 5/6, holding tank 7/8/9, SS bins A, SS bins B, mixer, online filtration, filling line 4
Sucralfate	Manufacturing tank 5/6, holding tank 7/8/9, SS bins A, SS bins B, mixer B, online filtration, filling line 4
Mebendazole	Manufacturing tank 5/6, holding tank 7/8/9, SS bins A, SS bins B, mixer B, online filtration, sieve 630 µ, filling line 4
Nystatin	Manufacturing tank 5/6, holding tank 7/8/9, SS bins A, SS bins B, mixer B, online filtration, filling line 4
Terfenadine	Manufacturing tank 5/6, holding tank 7/8/9, SS bins A, SS bins B, mixer B, online filtration, filling line 4
Kaolin II	Manufacturing tank 5/6, holding tank 7/8/9, SS bins A, SS bins B, mixer B, online filtration, filling line 4
Albendazole	Manufacturing tank 5/6, holding tank 7/8/9, SS bins A, SS bins B, mixer, online filtration, filling line 4

CLV-26

Worst-Case Products (Suspension)

Your Company's Logo

Your Company's Name

For manufacturing tank MF-06; holding tank numbers 7, 8, and 9; and filling line number 4

Products	Justification for Worst Case
Al–Mg hydroxide plus	Less solubility (7), least soluble
	Al hydroxide
	Mg hydroxide
	Simethicone
Ibuprofen	High toxicity level (LD_{50} 636 mg/kg oral rat)
Kaolin	Maximum daily dosage (5.4 g/day)

CLV-27

Product Grouping Matrix (Drops)

Your Company's Logo

Your Company's Name

Product	Ingredients	Batch Size (L)	Maximum Usage per Day	Toxicity Level LD_{50}	Solubility
Oxymetazoline 0.05%	Oxymetazoline HCl	2500	3 mg/day	0.88 mg/kg oral rat	2
Paracetamol	Paracetamol	2500	300 mg/day	2404 mg/kg oral rat	3
Vitamins A and D	Vitamin A	2000	1.0 mL/day	7919 mg/kg oral rat	7
	Vitamin D				
Pipenzolate	Pipenzolate methyl bromide	2500	12 mg/day	916 mg/kg oral rat	3
Multivitamins	Vitamin A	1000	500 IU	7910 mg/kg oral rat	7
	Vitamin D		400 IU	>2000 mg/kg oral rat	
	Vitamin E		0.528 mg/day	10,000 mg/kg oral rat	7
	Thiamine HCl		1.5 mg/day	>10,000 mg/kg oral rat	2
	Pyridoxine HCl		10 mg/day		1
	Nicotinamide		0.5 mg/day	3500 mg/kg oral rat	2
Saline	Sodium chloride	1000	2 drops (1 mg)	3000–4000 mg/kg oral rat	2
Iron	Ferrous sulfate	1000	375 mg/day	1520 mg/kg oral mouse	2
Metoclopramide	Metoclopramide HCl	250	1.8 mg/day	280 mg/kg oral mouse	1
Xylometazoline 0.01%	Xylometazoline HCl	100	2–3 times daily	230 mg/kg oral rat	3

CLV-28

Product/Equipment Train (Drops)

Your Company's Logo

Your Company's Name

Product	Equipments
Oxymetazoline 0.05%	Manufacturing tank 07, holding tank 10/11, SS bins A, SS bins B, mixer B, vessel 300, online filtration, filling line 5
Paracetamol	Manufacturing tank 07, holding tank 10/11, SS bins A, SS bins B, mixer B, vessel 300, online filtration, filling line 5
Vitamins A and D	Manufacturing tank 07, holding tank 10/11, SS bins A, SS bins B, mixer, vessel 300, online filtration, filling line 5
Pipenzolate	Manufacturing tank 07, holding tank 10/11, SS bins A, SS bins B, mixer, vessel 300, online filtration, filling line 5
Mix vitamins	Manufacturing tank 07, holding tank 10/11, SS bins A, SS bins B, mixer, mixer B, vessel 300, online filtration, filling line 5
Saline	Vessel 300, SS bins A, SS bins B, online filtration, holding tank 10/11, filling line 5
Ferrous sulfate	Manufacturing tank 07, holding tank 10/11, SS bins A, SS bins B, mixer, mixer B, vessel 300, online filtration, filling line 5
Metoclopramide	Manufacturing tank 07, holding tank 10/11, SS bins A, SS bins B, mixer, mixer B, vessel 300, online filtration, filling line 5
Xylometazoline 0.01%	Manufacturing tank 07, holding tank 10/11, SS bins A, SS bins B, mixer, mixer B, vessel 300, online filtration, filling line 5

CLV-29

Worst-Case Products (Drops)

Your Company's Logo

Your Company's Name

For manufacturing tank MF-07, filling line number 5, and holding tank numbers 10 and 11

Products	Justification for Worst Case
Mix vitamins	Less solubility (7), least soluble (vitamin A)
Oxymetazoline 0.05%	High toxicity level (LD_{50} 0.88 mg/kg oral rat)
Ferrous sulfate	Maximum daily dosage (375 mg/day)

Validation of oxymetazoline 0.05% drops will also validate the cleaning for maximum batch size, which is 2500 L.

CLV-30

Cleaning Validation Product Grouping Matrix (Cream/Ointment)

Your Company's Logo

Your Company's Name

Product	Ingredients	Batch Size (kg)	Toxicity Level LD_{50}	Solubility
Betamethasone[a]	Betamethasone valerate	1000	>3 g/kg oral rat	7
	Liquid paraffin			7
	Soft paraffin			7
Gentamicin[a]	Gentamicin sulfate	200	5 g/kg oral rat	7
Neomycin[a]	Nystatin	1000	10,000 mg/kg oral rat	7
	Neomycin sulfate		8.0 g/kg oral mouse	2
	Gramicidin			7
	Triamcinolone acetonide			7
Hydrocortisone[a]	Hydrocortisone	1000		7
	Soft paraffin			7
	Liquid paraffin			7
	Sorbitan sesquioleate			7
Cinchocaine ointment	Cinchocaine HCl	200	42 mg/kg oral rat	1
	Betamethasone valerate		>3 g/kg oral rat	7
Nystatin[a]	Nystatin topical	1000	10,000 mg/kg oral rat	7
Fusidic acid[a]	Fusidic acid	1000	1500 mg/kg oral mouse	7
Acyclovir[a]	Acyclovir	15	>20.0 g/kg oral rat	5
Tribenoside/lidocaine[a]	Tribenoside/lidocaine HCl	250	>10 mg/kg oral rat	7
			292 mg/kg oral mouse	1
Fluticasone propionate[a]	Fluticasone propionate	1000	>2000 mg/kg oral rat	7
	White soft paraffin			7
	Hard paraffin			7
	Sorbitan sesquioleate			7
	Propylene glycol			7
	Microcrystalline wax			7
Clobetasol[a]	Clobetasol propionate	1000	>3 g/kg oral rat	7
Propionate 0.05%	Sorbitan sesquioleate			7
	Propylene glycol			6

[a] Products manufactured in both cream and ointment forms.

Your Company's Logo

Your Company's Name

30.1 Ointments

Product	Ingredients	Batch Size (kg)	Toxicity Level LD_{50}	Solubility
Tetracycline	Tetracycline HCl	750	6443 mcg/kg oral rat	3
Lidocaine	Lidocaine	750	292 mg/kg oral mouse	1
Oxytetracycline	Oxytetracycline	200	680 mg/kg oral rat	2

For cleaning validation study, ointment would be considered as worst case due to their oily nature.

CLV-31

Product/Equipment Train (Cream and Ointment)

Your Company's Logo

Your Company's Name

Product	Equipments
Betamethasone[a]	Manufacturing vessel, melting vessel, SS container, homogenizer, filling line
Gentamicin[a]	Manufacturing vessel, melting vessel, SS container, homogenizer, stirrer, filling line
Neomycin/nystatin[a]	Manufacturing vessel, melting vessel, SS container, homogenizer, water bath, UT homogenizer, probost and class homogenizer, filling line
Hydrocortisone[a]	Manufacturing vessel, melting vessel, SS container, homogenizer, stirrer, filling line
Cinchocaine/betamethasone ointment	Manufacturing vessel, melting vessel, SS container, UT homogenizer, filling line
Nystatin[a]	Manufacturing vessel, melting vessel, SS container, probost and class homogenizer, filling line
Fusidic acid[a]	Manufacturing vessel, melting vessel, SS container, probost and class homogenizer, filling line
Acyclovir[a]	Manufacturing vessel, melting vessel, SS container, probost and class homogenizer, filling line
Tribenoside/lidocaine[a]	Manufacturing vessel, melting vessel, SS container, homogenizer, filling line
Fluticasone propionate[a]	Manufacturing vessel, melting vessel, SS container, UT homogenizer, filling line
Clobetasol propionate[a] 0.05%	Manufacturing vessel, melting vessel, SS container, UT homogenizer, filling line
Tetracycline	Manufacturing vessel, melting vessel, SS container, filling line
Lidocaine	Manufacturing vessel, melting vessel, SS container, stirrer, polyester filter
Oxytetracycline	Manufacturing vessel B, melting vessel, SS container, filling line

[a] Products manufactured in both cream and ointment forms.

For cleaning validation study, ointment would be considered as worst case due to their oily nature.

Your Company's Logo

Your Company's Name

31.1 Cream Products

Product	Equipments
Diethylamine/chlorobutol	Manufacturing vessel, melting vessel, SS container, homogenizer, filling line
Miconazole nitrate	Manufacturing vessel, melting vessel, SS container, homogenizer, filling line
Diclofenac gel	Manufacturing vessel, melting vessel, SS container, homogenizer, stirrer, SS sieve, filling line
Zinc oxide cream	Manufacturing vessel, melting vessel, SS container, homogenizer, stirrer, filling line
Dexpanthenol cream	Manufacturing vessel, melting vessel, SS container, homogenizer, stirrer, filling line
Fusidic/betamethasone cream	Manufacturing vessel, melting vessel, SS container, homogenizer, stirrer, filling line
Miconazole nitrate cream	Manufacturing vessel, melting vessel, SS container, homogenizer, stirrer, filling line
Ibuprofen cream	Manufacturing vessel, melting vessel, SS container, homogenizer, stirrer, filling line
Silver sulfadiazine cream	Manufacturing vessel, melting vessel, SS container, UT homogenizer, stirrer, filling line

CLV-32

Worst-Case Products (Ointment and Cream)

Your Company's Logo

Your Company's Name

32.1 Ointments

Products	Justification for Worst Case
Cinchocaine/betamethasone	High toxicity level (LD_{50} 42 mg/kg oral bird)
Fluticasone	Less solubility (7), least soluble six ingredients (steroids)

32.2 Creams

Products	Justification for Worst Case
Diclofenac cream	High toxicity level (LD_{50} 150 mg/kg oral rat)

CLV-33

Product Grouping Matrix (Suppositories)

Your Company's Logo

Your Company's Name

Product	Ingredients	Batch Size (kg)	Maximum Usage per Day (mg)	Toxicity Level LD_{50}	Solubility
Paracetamol 500 mg	Paracetamol	76	1000	2404 mg/kg oral rat	3
Metoclopramide	Metoclopramide	72	20	280 mg/kg oral rat	1
Diclofenac	Diclofenac sodium	144	150	4067 mg/kg oral rat	4
Betamethasone	Betamethasone valerate	144	2	280 mg/kg oral rat	1
	Cinchocaine HCl		2	>3 g/kg oral rat	7
Tribenoside	Tribenoside	148	800	>10 mg/kg oral rat	7
	Lidocain HCl		80	292 mg/kg oral mouse	1
Miconazole	Miconazole nitrate	152		640 mg/kg oral rat	5
Bisacodyl 10 mg	Bisacodyl	144	10	4320 mg/kg oral rat	7
Glycerin	Glycerin	147	3600	17,000–27,000 mg/kg oral rat	Miscible in water

CLV-34

Cleaning Validation Product/Equipment Train (Suppositories)

Your Company's Logo

Your Company's Name

Product	Equipments
Paracetamol 500 mg	Manufacturing vessel 250, melting vessel, storage vessel, SS container, filling line
Metoclopramide	Manufacturing vessel 250, melting vessel, premix vessel, storage vessel, SS container, filling line
Diclofenac	Manufacturing vessel 250, melting vessel, premix vessel, storage vessel, SS container, filling line
Betamethasone valerate	Manufacturing vessel 250, melting vessel, premix vessel, storage vessel, SS container, filling line
Tribenoside/lidocaine HCl	Manufacturing vessel 250, melting vessel, premix vessel, storage vessel, SS container, filling line
Miconazole nitrate	Manufacturing vessel 250, melting vessel, premix vessel, storage vessel, SS container, filling line
Laxocodyl 10 mg	Manufacturing vessel 250, melting vessel, premix vessel, storage vessel, SS container, filling line
Laxolyne	Manufacturing vessel 250, melting vessel, premix vessel, storage vessel, SS container, filling line

CLV-35

Worst-Case Products (Suppositories)

Your Company's Logo

Your Company's Name

Products	Justification for Worst Case
Tribenoside/lidocaine HCl	High toxicity >10 mg/kg oral rat (tribenoside)
Laxolyne	Maximum daily dose 3600 mg/day
Laxocodyl	Less solubility 7 (bisacodyl)

CLV-36

Cleaning Validation Protocols Products (Suppositories)

CLV-36.1

Protocol for Manufacturing Vessel

Your Company's Logo

Your Company's Name

ABC Pharmaceutical Company	**CLEANING VALIDATION PROTOCOL** **Equipment Name**	
	Issued on: **Date**	**Protocol Number** **CLVL-000**
	Location **Soft Product Compounding**	

Equipment Name ..... **Manufacturing Vessel**

Model..... **Model**

Capacity ..... **1000 L**

Manufacturer..... **Company, Country**

Written by	**Signature & Date**
Validation Officer	_____
Reviewed by	**Signature & Date**
Manager QA	_____
	Signature & Date
Production Manager	_____
	Signature & Date
QC Manager	_____
Authorized by	**Signature & Date**
QA Director	_____

Your Company's Logo **Your Company's Name**

36.1.1 Objective

The objective of this protocol is to demonstrate that the cleaning procedure will successfully and consistently reduce the level of residues to a predetermined level of acceptability for the 1000-L manufacturing vessel.

36.1.2 Scope

This protocol will cover cleaning of the semisolid manufacturing vessel (Figure 36.1.1) for the following cream and ointment products (Table 36.1.1).

The above-mentioned products are divided into different categories (group) based on water solubility, toxicity, and batch size. From each group, one worst-case products analyzed for cleaning validation (Table 36.1.2).

Since a natural herb is manufactured in both ointment and cream forms, the cleaning procedure for the ointment is deemed sufficient to meet the criteria for both the dosage forms due to more difficult cleaning of the oily product (ointment).

Based on the criteria mentioned above, selection of natural herb ointment and oxytetracycline ointment as worst cases for less solubility and high toxicity, respectively, will also validate the cleaning procedure for cream products. However, to further enhance the

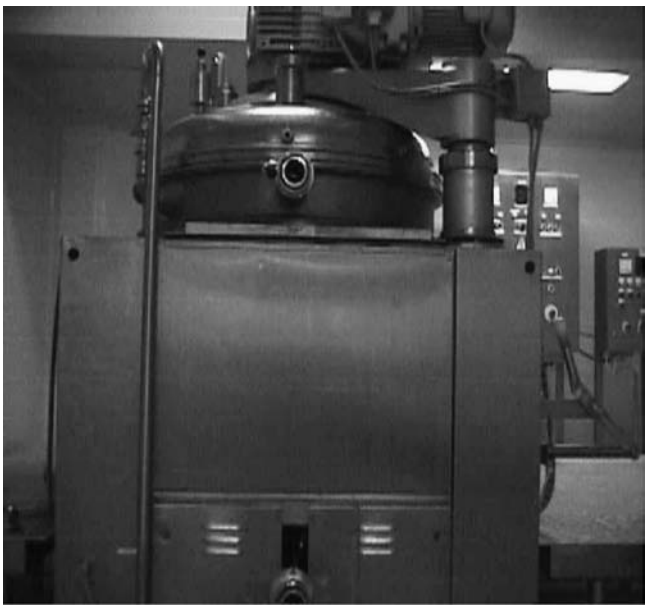


FIGURE 36.1.1
1000-L manufacturing vessel.

Your Company's Logo

Your Company's Name

TABLE 36.1.1

Product Matrix

Product	Active Ingredient/s	Batch Size	Toxicity LD_{50}	Solubility Scale[a]
Ointment/Cream				
Betamethasone[b]	Betamethasone valerate	1000	>3 g/kg oral rat	7
Gentamicin[b]	Gentamicin sulfate	200		
Nystatin,[b] neomycin sulfate	Nystatin, neomycin sulfate, gramicidin, triamcinolone acetonide	1000	10,000 mg/kg oral rat	7
			8.0 g/kg oral mouse	2
				7
				7
Hydrocortisone[b]	Hydrocortisone	1000		7
Cinchocaine HCl ointment	Cinchocaine HCl, Betamethasone valerate	200		1
			>3 g/kg oral rat	7
Nystatin topical[b]	Nystatin topical	1000	10,000 mg/kg oral rat	7
Fusidic acid[b]	Fusidic acid	1000		7
Acyclovir[b]	Acyclovir	15	>20 g/kg oral rat	5
Tribenoside,[b] lidocaine HCl	Tribenoside, lidocaine HCl	250	>10 mg/kg oral rat	7
			292 mg/kg oral mouse	1
Natural herbs[b]	Natural herbs	1000	Nontoxic	
Oxytetracycline	Oxytetracycline	200	680 mg/kg oral rat	2
Fluticasone propionate[b]	Fluticasone propionate	1000		7
Clobetasol propionate[b]	Clobetasol propionate	1000	>3 g/kg oral rat	7
Ointment[c]				
Tetracycline HCl	Tetracycline HCl	750	6443 mcg/kg oral rat	3
Lidocaine	Lidocaine	750	292 mg/kg oral mouse	1
Cream Products				
Cream A	Diethylamine salicyclate, chlorobutol, menthol	1000		4
Miconazole nitrate	Miconazole nitrate	1000		6
Diclofenac sodium	Diclofenac sodium	1000	150 mg/kg oral rat	4
Zinc oxide cream	Zinc oxide	1000		7
Dexpanthenol cream	Dexpanthenol	1000		2
Fusidic acid, betamethasone cream	Fusidic acid, betamethasone valerate	1000		7
			>3 g/kg oral rat	7

Your Company's Logo **Your Company's Name**

TABLE 36.1.1 (continued)

Product Matrix

Product	Active Ingredient/s	Batch Size	Toxicity LD_{50}	Solubility Scale[a]
Miconazole nitrate cream	Miconazole nitrate	1000		6
Ibuprofen cream	Ibuprofen	1000	636 mg/kg oral rat	7
Silver sulfadiazine Cream	Silver sulfadiazine	1000	>10,000 mg/kg oral rat	7

[a] Solubility key: 1. very soluble in water, 2. freely soluble in water, 3. soluble in water, 4. sparingly soluble in water, 5. slightly soluble in water, 6. only very slightly soluble in water, 7. practically insoluble in water or insoluble.

[b] Products manufactured in both cream and ointment form.

[c] For the cleaning validation study ointment dosage form would be considered as worst case due to its oily nature.

confidence, a high toxicity worst case is selected in cream products as well. Diclofenac sodium cream is most toxic (diclofenac sodium) in all the cream products; therefore, this product will be taken as another worst case for cleaning procedure validation.

Large batch size is also covered in the natural herbs ointment validation, which is 1000 kg; therefore a separate case of largest batch size will not be taken for validation.

36.1.3 Responsibilities

The following personnel are responsible for the execution of this protocol:

Validation officer/production officer/QA inspector/machine operator; for details, please refer to Attachment II.

TABLE 36.1.2

Worst Case for Manufacturing Vessel

Products	Justification for Worst Case
Ointment	
Natural herb	Less solubility (7), least soluble three actives
Oxytetracycline HCl	High toxicity level (LD_{50} 6.443 mg/kg oral rat)
Cream	
Diclofenac sodium cream	High toxicity level (LD_{50} 150 mg/kg oral rat)

Your Company's Logo Your Company's Name

36.1.4 Description of the Cleaning Process

The manufacturing vessel is cleaned manually as per SOP No. ABC-001.

1. Label the equipment "Under Cleaning"
2. Transfer the water and soap to the vessel by vacuum through the connected pipe
3. Set the vessel's temperature indicator at 90°C and start heating
4. Start the agitator and homogenizer at speed II, with recirculation
5. Continue mixing and homogenizing for a further 20 min after reaching 90°C
6. Connect the outlet valve of the vessel with a hose and drain out the washing in a 200-L stainless steel drum
7. Lift the vessel lid and clean thoroughly the agitator angles and the lower side of the lid with a sponge
8. Rinse the inside and the lower side of the lid of the vessel with purified water for 3 min by means of a 1" hose
9. Drain out the water in the drainage by means of a hose
10. Dismantle all the joints, valves, and pipes
11. Clean all joints, valves, and pipes with sponge wetted with 1% soap
12. Flush each part with purified water by means of a 1" hose for 30 s
13. Spray the inside and outside of the vessel with 70% alcohol
14. Label the vessel "Clean"
15. Make entries in the cleaning log and label the equipment "Clean" with the date of cleaning and signature of the supervisor as per SOP No. ABC-002

36.1.5 Identification of Critical Parameters

The critical parameters should be monitored as stated in Table 36.1.3.

TABLE 36.1.3

Critical Parameters

Parameters	Specification	Actual Reading
Temperature	90°C	
Time	20 min after 90°C	
Purified water volume	200 L	
Soap quantity	500 mL	

Your Company's Logo Your Company's Name

36.1.6 Description of the Sampling Process

36.1.6.1 Sampling Technique

The following sampling techniques are used to take the sample from the vessel:

a. Surface swabs (sterile cotton swabs wetted with purified water)
b. Water rinses (in clean bottle as listed below)

36.1.6.1.1 Surface Swabs

36.1.6.1.1.1 Procedure for Sampling

Sampling should be performed as per SOP No. ABC-003; the validation officer is responsible for taking the swab sample. Samples of the internal surfaces are taken by moistening the swab (ready-made sterile cotton swab) with a suitable solvent (purified water). Sample a 25-cm^2 area and place the swab in a test tube containing 10 mL of solvent (purified water). Swab sample from each part of manufacturing vessel is collected as per Table 36.1.4.

36.1.6.1.1.2 Sampling Precautions

Before taking the sample, wear

i. Hand gloves
ii. Face mask

TABLE 36.1.4

Surface Swabs Sampling Description

Description	Sample ID	Reference
Manufacturing vessel	S1	As per Figures 36.1.2 and 36.1.3
	S2	
	S3	
	S4	
	S5	
	S6	
	S7	
	S8	
	S9	
	S10	
	S11	
	S12	

Your Company's Logo **Your Company's Name**

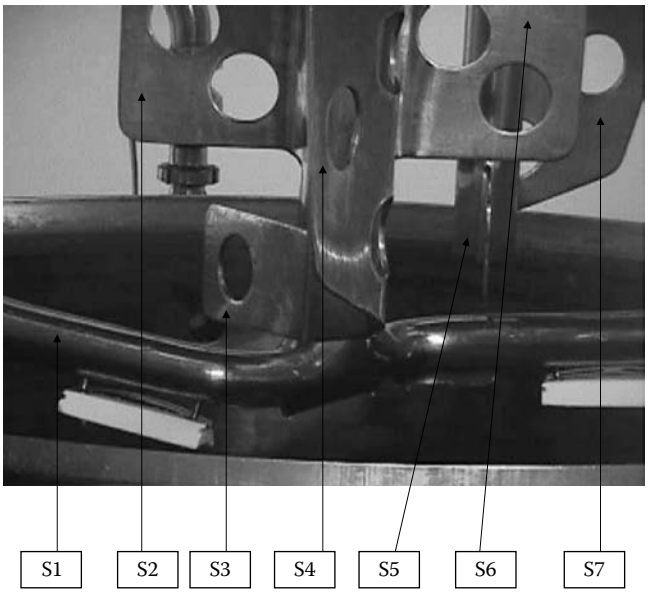


FIGURE 36.1.2
Mixer agitator.

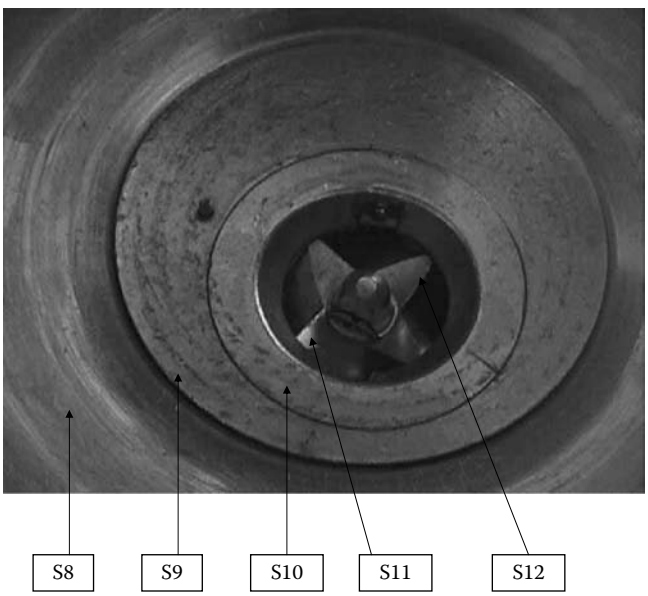


FIGURE 36.1.3
Vessel inner surface and mixer.

Your Company's Logo **Your Company's Name**

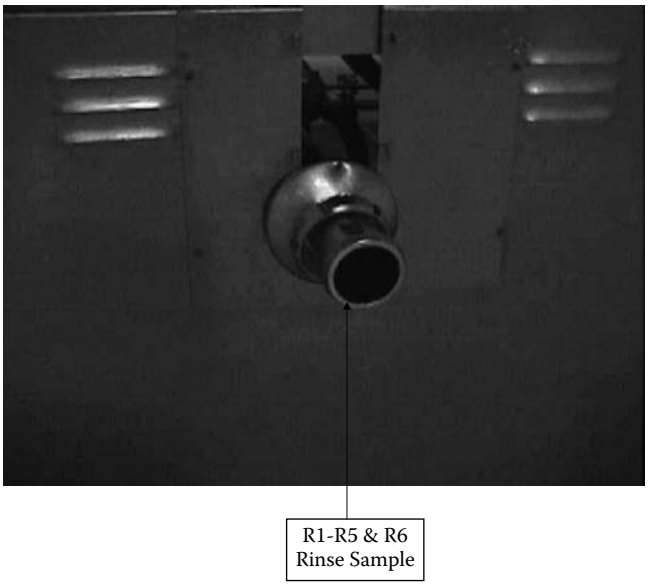


FIGURE 36.1.4
Rinse sampling point (bottom drain).

36.1.6.1.1.3 Rinse Sample

The rinse sampling technique is used to take samples from the vessel. After the completion of cleaning, take rinse samples from the bottom of the vessel sampling points (Figure 36.1.4) R1–R5 for the chemical analysis and R6 for bio-burden (Table 36.1.5).

36.1.6.1.1.4 Handling of Samples

Samples are kept in the refrigerator if not testing immediately

Analyze the samples within 2 h after collection for pH, conductivity, and TOC and detergent detection

TABLE 36.1.5
Rinse Sampling Description

Description	Sample Location	Sample ID
Manufacturing vessel	Bottom drain point	R1-pH
		R2-conductivity
		R3-TOC
		R4-detergent determination
		R5-MAC
		R6-bio-burden

Your Company's Logo **Your Company's Name**

HPLC analysis (maximum allowable carryover) and bio-burden must be performed within 24 h

36.1.7 Test Functions

36.1.7.1 Visual Inspection

Inspection of cream and ointment manufacturing vessel is performed visually. The vessel should be clean and free from any traces of residues. For detailed information about sample ID, volume, testing specification, and testing method, see the sampling and testing plan in Table 36.1.6.

36.1.8 Verification of Documents

i. Verify the cleaning procedure No. ABC-001.
ii. Verify the vessel's cleaning logbook records.
iii. Verify the staff training record (refer to Attachment IV).

36.1.9 Documentation

i. All analysis results are recorded in the analysis logbook.
ii. Printouts and chromatograms are attached to the validation report and a copy of that is also attached to the analytical logbook.
iii. All analysis and data should be verified by a second analyst.

TABLE 36.1.6

Sampling and Testing Plan

S. No.	Test	Identification Labeling	Sample Volume	Sampling Bottle	Testing Specifications	Testing Method/ Procedure No.
1	pH	R1-pH	100 mL	Clean bottle	5–7 pH unit	STM-PL-001
2	Conductivity	R2-conductivity	100 mL	Clean bottle	NMT 5.0 µs/cm	
3	TOC	R3-TOC	50 mL	Clean bottle	NMT 500 ppb	SOP-ABC-004
4	MAC	R4-MAC	50 mL	Clean bottle	NMT MAC	Validated HPLC method
5	Bio-burden	R5-microbiology	100 mL	Sterilized bottle	NMT 10 cfu/100 mL	STM-MC-001

iv. All training records are checked by the validation officer.
v. The final report for cleaning validation should be prepared by the validation officer.

36.1.10 Acceptance Criteria

a. *Visual inspection:* The visible internal equipment surfaces and all critical and difficult-to-clean parts are optically free from residue and the color of the final rinse water is comparable to DIW.
b. *pH determination:* The pH value of the rinse should be in between 5 and 7 and comparable to DIW pH value.
c. *Conductivity:* The conductivity of the rinse should not be more than the conductivity of the blank DIW sample kept under the same conditions.
d. *Total organic carbon:* The TOC of the final rinse should be comparable to the blank DIW sample kept under the same conditions (DIW TOC limit is NMT 500 ppb).
e. *Detergent detection:* No foam is detected on top of the rinse sample after testing.
f. *Maximum allowable carryover:* The active ingredient in the final rinse is either not detected or is equal to or less than the MAC (calculated theoretically for product).

   Based on the solubility and maximum daily dose matrix, the MAC is calculated for each product. The MAC is calculated as follows:

$$\text{MAC} = \frac{\text{TD} \times \text{BS} \times \text{SF}}{\text{LDD}},$$

   where MAC is the maximum allowable carryover, TD is a single therapeutic dose, BS is the batch size of the next product to be manufactured in the same equipment, SF is the safety factor, and LDD is the largest daily dose of the next product to be manufactured in the same equipment.

   The calculated value is the maximum amount of active ingredient of a certain product that is allowed to be carried over to the next batch.
g. *Bio-burden:* The bio-burden should not be more than 10 cfu/100 mL for the rinses.

Your Company's Logo **Your Company's Name**

36.1.11 List of Attachments

Attachment I	Description of equipment and product
Attachment II	Cleaning/testing responsibilities
Attachment III	Training record verification
Attachment IV	Rinse analysis results
Attachment V	Swab analysis results

Your Company's Logo **Your Company's Name**

Attachment I

Description of Equipment and Product

Equipment Name: _____

Serial No.: _____

Capacity: _____

Location: _____

Room No.: _____

Previous Product: _____

Batch No. of Previous Product: _____

Manufacturing Date: _____

Active Ingredient: _____

Therapeutic Group: _____

Cleaning Date: _____

Cleaning SOP No.: _____ Revision No.: _____

Sampling Technique: _____

Cleaning Sample Analysis Date/Time: _____ Result: _____

Test Method Reference: _____ Reference Analytical Logbook: _____

Limit of Detection: _____ Safety Factor: _____

Next Product to Be Manufactured in the Same Equipment: _____

Performed by: _____ Date: _____

Checked by: _____ Date: _____

Your Company's Logo **Your Company's Name**

Attachment II

Cleaning/Testing Responsibilities

Cleaning/Testing	Done By	Recorded On	Checked By
Equipment cleaning	Machine operator	Equipment usage/ cleaning logbook	Production manager
Visual inspection	Validation officer	Analytical logbook	Manager QA
Rinse sample	Machine operator/validation officer	Sampling sheet	Manager QA
pH/detergent	Validation officer/QC analyst	Analytical logbook	QA/QC officer
Conductivity	Validation officer/QC analyst	Analytical logbook	QA/QC officer
TOC	Validation officer/QC analyst	Analytical logbook	QA/QC officer
MAC	Validation officer/QC analyst	Analytical logbook	QC officer
Bio-burden	Validation officer/QC microbiologist	Analytical logbook	Manager QC, Microbiology

TOC, total organic carbon; MAC, maximum allowable carryover.

Performed by: _____ Date: _____

Checked by: _____ Date: _____

Your Company's Logo **Your Company's Name**

Attachment III

Training Record Verification

The following staff were found trained on cleaning of equipment.

Using SOP No. ABC-004; Revision No.; Issued on; Date

Name:_____ ID No.:_____ Sign.:_____ Date:_____

Name:_____ ID No.:_____ Sign.:_____ Date:_____

Performed by: _____ Date: _____

Checked by: _____ Date: _____

Your Company's Logo **Your Company's Name**

Attachment IV

Rinse Analysis Results

Sampling ID	Blank DIW			Rinse Sample					
	pH	**Conductivity**	**TOC**	**MAC HPLC Result**	**pH (Limit 5–7)**	**Conductivity NMT 5.0 µs/ cm at 25°C**	**TOC NMT 500 ppb**	**Detergent Determi-nation**	**Bio-Burden**
R1–R5									
R6									
HPLC chromatogram printouts should be attached to the analytical logbook.									

Performed by: _____ Date: _____

Checked by: _____ Date: _____

Your Company's Logo **Your Company's Name**

Attachment V

Swab Analysis Results

Performed by: _____ Date: _____

Sampling Location/ID	Visual Inspection	Carryover HPLC Result per 25 cm^2	Total Carryover
S1			
S2			
S3			
S4			
S5			
S6			
S7			
S8			
S9			
S10			
S11			
S12			

Checked by: _____ Date: _____

CLV-36.2

Protocol for Bin-Washing Station

Your Company's Logo

Your Company's Name

ABC Pharmaceutical Company	**CLEANING VALIDATION PROTOCOL** **Equipment Name**	
	Issued on **Date**	**Protocol Number** **CLVL-000**
	Location **Washing Area**	

Equipment ..... **Bin-Washing Station**

Model ..... **Model**

Manufacturer ..... **Company, Country**

Written by — **Signature & Date**

Validation Officer _____

Reviewed by — **Signature & Date**

Manager QA _____

Signature & Date

Production Manager _____

Signature & Date

QC Manager _____

Authorized by — **Signature & Date**

QA Director _____

Your Company's Logo

Your Company's Name

36.2.1 Objective

The objective of this protocol is to demonstrate that the cleaning procedures ABC-001 and ABC-002 will successfully and consistently reduce the level of residues to a predetermined level of acceptability for the production bins by an automatic washing station.

36.2.2 Scope

This protocol will cover the cleaning process of the manufacturing bins by automatic washing station series for all syrup, drops, and suspension products (Table 36.2.1).

Note: Worst-case products selected for the bins are one worst product from each dosage form, namely syrup, drops, and suspension.

36.2.3 Responsibilities

The following personnel are responsible for the execution of this protocol:

Validation officer/production officer/QA inspector and machine operator; for details, please refer to Attachment II.

TABLE 36.2.1

Worst-Case Product

Product	Active Ingredient/s	Batch Size (L)	Maximum Dosage/day	Toxicity LD_{50} (mg/kg oral rat)	Solubility Scale
Paracetamol syrup	Paracetamol	7500	60 mg/day	2404	3
Vitamin drops	Vitamin A	1000	500 IU	7910	7
	Vitamin D		400 IU	>2000	
	Vitamin E		0.528 mg/day	10,000	7
	Thiamine HCl		1.5 mg/day	>10,000	2
	Pyridoxine HCl		10 mg/day		1
	Nicotinamide		0.5 mg/day	3500	2
Ibuprofen suspension	Ibuprofen	7500	800 mg	636	7

Your Company's Logo **Your Company's Name**

36.2.4 Description of the Process

The automatic washing station is cleaned manually as per SOP No. ABC-001 and operated as per SOP No. ABC-002.

1. Place a label explaining the status of "UNDER CLEANING" before the process
2. Wipe the surface of the washing station and the shield for the pump room with filtered 70% alcohol
3. Clean the electrical panel and trunk with alcohol
4. Mop the bottom of the washing station with disinfectant solution
5. Enter the details in the respective logbook
6. Contact the production supervisor to check the cleanliness
7. Place a label stating the status "CLEAN" after obtaining the approval from the QA inspector

36.2.5 Identification of Critical Parameters

The critical parameters should be monitored as stated in Table 36.2.2.

36.2.6 Description of the Sampling Process

36.2.6.1 Sampling Technique

The following sampling technique is used to take samples from bins after washing the automatic washing station.

TABLE 36.2.2

Critical Parameters

Parameters	Specification	Actual Reading
Temperature	60°C	
Time	45 min	
DIW volume	25 L	
Number of cycle	Cycle No. 1	
Cleaning material	Liquid soap	

Your Company's Logo Your Company's Name

36.2.6.1.1 Surface Swabs (Sterile Cotton Swabs Wetted with WFI)

36.2.6.1.1.1 Procedure for Sampling

Sampling should be performed as per SOP No. ABC-003; the validation officer is responsible for taking the swab sample. Samples of the internal surfaces are taken by moistening the swab (ready-made sterile cotton swab) with a suitable solvent (DIW). Sample a 25-cm^2 area and place the swab in a test tube containing 10 mL of solvent (DIW). Swab samples from each part of the SS bins are collected as per Table 36.2.3.

36.2.6.1.1.2 Sampling Precautions

Before taking samples, wear

i. Hand gloves
ii. Face mask

36.2.6.1.1.3 Handling of Samples

Samples should be kept in the refrigerator, if not testing immediately

Analyze the samples within 2 h after collection for detergent detection

HPLC analysis (MAC) and bio-burden should be performed within 24 h

36.2.7 Test Functions

a. *Visual inspection:* Inspection of bins is performed visually.
b. *Detergent detection:* The test for the detergent detection is performed as per procedure No. ABC-004.
c. *Maximum allowable carryover:* The test for the MAC of the swabs is performed as per the HPLC method suitable for each product residue.

   Note: The validated HPLC test method is used for the determination of chemical residues.

TABLE 36.2.3

Surface Swabs Sampling Description for SS Bins after Cleaning by Automatic Bin-Washing Station

Description	Sample Location	Sample ID	Reference
SS bins automatic washing station	Inside left top	S1	Attachment III-pictures and sampling locations
	Inside right top	S2	
	Inside left bottom	S3	
	Inside left bottom	S4	
	Bottom middle	S5	
	Inside left corner top	S6	
	Inside right corner top	S7	

Your Company's Logo **Your Company's Name**

d. *Bio-burden:* The test for bio-burden is performed as per STM No. MC-0065 by the Microbiology section.

36.2.8 Verification of Documents

i. Verify the bin-washing station cleaning procedure.
ii. Verify the bin-washing station cleaning logbook records.
iii. Verify the staff training record (Refer to Attachment VI).

36.2.9 Documentation

i. All analysis results are recorded in the analysis logbook.
ii. Printouts and chromatograms are attached to the validation report and a copy of that is also attached to the analytical logbook.
iii. All analysis and data are verified by a second analyst.
iv. All training records are checked by the QA officer.
v. Final report for cleaning validation should be prepared by the QA officer.

36.2.10 Acceptance Criteria

a. *Visual inspection:* The visible internal equipment surfaces and all critical and difficult-to-clean parts are optically free from residue.
b. *Detergent detection:* No foam is detected on top of the rinse sample after testing.
c. *Maximum allowable carryover:* The active ingredient in the swabs is either not detected or equal to or less than the MAC (calculated theoretically for product).

Based on the solubility and maximum daily dose matrix, the MAC is calculated for each product. The MAC is calculated as follows:

$$\text{MAC} = \frac{\text{TD} \times \text{BS} \times \text{SF}}{\text{LDD}},$$

where MAC is the maximum allowable carryover, TD is a single therapeutic dose, BS is the batch size of the next product to be manufactured in the same equipment,

Your Company's Logo **Your Company's Name**

SF is the safety factor, LDD is the largest daily dose of the next product to be manufactured in the same equipment.

The calculated value is the maximum amount of active ingredient of a certain product that is allowed to be carried over to the next batch.

d. *Bio-burden:* The bio-burden should not be more than 10 cfu/swab.

36.2.11 List of Attachments

Attachment I	Description of equipment and product
Attachment II	Cleaning/testing responsibilities
Attachment III	Bin pictures and sampling location
Attachment IV	Sampling and testing plan
Attachment V	Swab sampling calculation
Attachment VI	Training record verification
Attachment VII	Swab analysis results

Your Company's Logo **Your Company's Name**

Attachment I

Description of Equipment and Product

Equipment Name: _____

Serial No.: _____

Capacity: _____

Location: _____

Room No.: _____

Previous Product: _____

Batch No. of Previous Product: _____

Manufacturing Date: _____

Active Ingredient: _____

Therapeutic Group: _____

Cleaning Date: _____

Cleaning SOP No.: _____ Revision No.: _____

Sampling Technique: _____

Cleaning Sample Analysis Date: _____ Assay Result: _____

Test Method Reference: _____ Reference Analytical Logbook: _____

Limit of Detection: _____ Safety Factor: _____

Performed by: _____ Date: _____

Checked by: _____ Date: _____

Worst-Case Products

- ☐ Paracetamol syrup
- ☐ Vitamin drops
- ☐ Ibuprofen suspension

Your Company's Logo **Your Company's Name**

Attachment II

Cleaning/Testing Responsibilities

Cleaning/Testing	Done By	Recorded On	Checked By
Equipment cleaning	Machine operator	Equipment usage/ cleaning logbook	Production manager
Detergent determination	Validation officer/QC analyst	Analytical logbook	QC analyst
MAC	Validation officer/QC analyst	Analytical logbook	QC section head
Bio-burden	Validation officer/microbiologist	Analytical logbook	QC manager Micro-lab

MAC, maximum allowable carryover.

Performed by: _____ Date: _____

Checked by: _____ Date: _____

Your Company's Logo **Your Company's Name**

Attachment III

Bin Pictures and Sampling Location

FIGURE 36.2.1
Bin-washing station (front view).

FIGURE 36.2.2
Bin-washing station (side view).

Your Company's Logo **Your Company's Name**

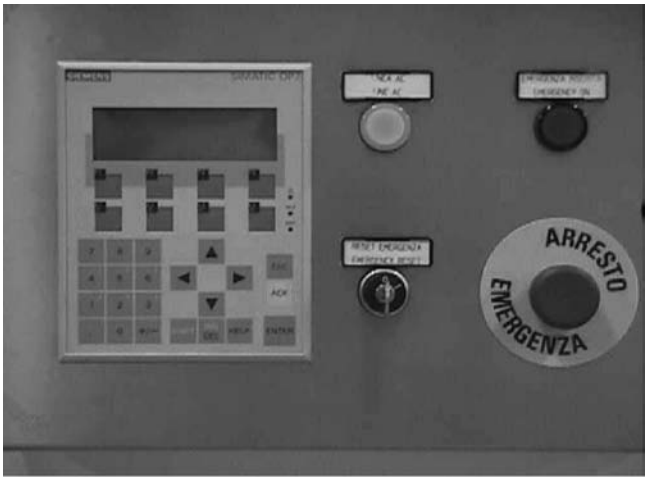


FIGURE 36.2.3
Bin-washing station (control panel).

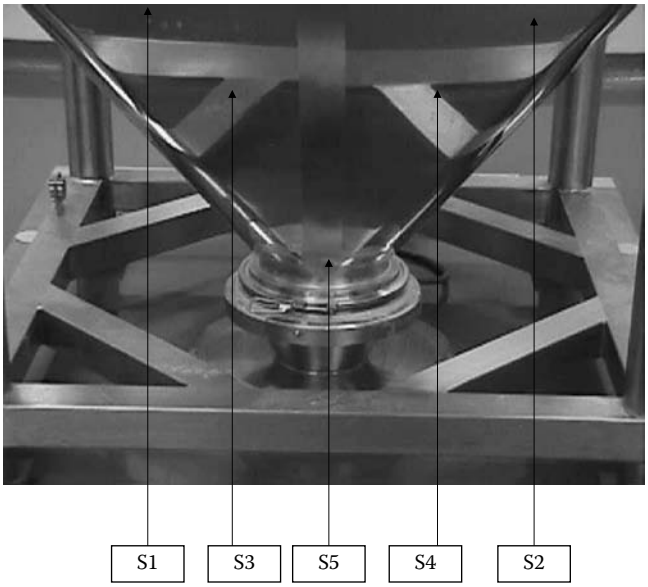


FIGURE 36.2.4
Bin sampling location.

Your Company's Logo **Your Company's Name**

FIGURE 36.2.5
Bin sampling location.

Your Company's Logo **Your Company's Name**

Attachment IV

Sampling and Testing Plan

Process Description: _____

Process Involved: _____

Worst-Case Products

- ☐ Paracetamol syrup
- ☐ Vitamin drops
- ☐ Ibuprofen suspension

Sampling Location	Sampling Property		Type of Sample	Sample Area (cm^2)
	D	N	S*	
S1 (inside left top)	_	✓	S	25
S2 (inside right top)	_	✓	S	25
S3 (inside right bottom)	_	✓	S	25
S4 (inside left bottom)	_	✓	S	25
S5 (bottom surface)	_	✓	S	25
S6 (corner left side top)	✓	_	S	25
S7 (corner right side top)	✓	_	S	25

D, difficult to clean; N, normal; S*, swab.

Performed by: _____ Date: _____

Checked by: _____ Date: _____

Your Company's Logo **Your Company's Name**

Attachment V

Calculation for Surface Swabs

$$\text{MAC} = \frac{\text{TD} \times \text{BS} \times \text{SF}}{\text{LDD}}$$

Calculation:

$$Y = X \times \text{surface area},$$

where Y is the active ingredient on the corresponding equipment part, X is the active ingredient recovered from 25 cm^2 by swab from the corresponding equipment part, and surface area is the area of corresponding equipment parts A–G:

$$Z = Y1 + Y2 + Y3 + Y4 + Y5 + Y6 + Y7,$$

where Z is the total active ingredient recovered from the machine, Y1 is the active ingredient recovered from part S1, Y2 is the active ingredient recovered from part S2, Y3 is the active ingredient recovered from part S3, Y4 is the active ingredient recovered from part S4, Y5 is the active ingredient recovered from part S5, Y6 is the active ingredient recovered from part S6, and Y7 is the active ingredient recovered from part S7.

Acceptance criteria:

$$Z \leq \text{MAC}.$$

Your Company's Logo **Your Company's Name**

Attachment VI

Training Record Verification

The following staff were found trained on cleaning of equipment.

Using SOP No. ABC-005; Revision No.; Issued on; Date

ABC-002 Revision No.; Issued on; Date

Name: _____ ID No.: _____ Sign.: _____ Date: _____

Name: _____ ID No.: _____ Sign.: _____ Date: _____

Training Record Verification (Analyst)

The following analyst trained on STM No. _____

Name: _____ ID No.: _____ Sign.: _____ Date: _____

Performed by: _____ Date: _____

Checked by: _____ Date: _____

Your Company's Logo **Your Company's Name**

Attachment VII

Worst-Case Products

- ☐ Paracetamol syrup
- ☐ Vitamin drops
- ☐ Ibuprofen suspension

Swab Analysis Results

Sampling Location	Visual Inspection	Detergent Detection	Bio-Burden Test NMT 33 cfu/swab	Carryover HPLC Result per 25 cm^2 (X)	Carryover 25 cm^2 ×Surface Area Total Carryover Y = X × (A – G)
S1					
S2					
S3					
S4					
S5					
S6					
S7					

Performed by: _____ Date: _____

Checked by: _____ Date: _____

CLV-36.3

Cleaning Validation Protocol for Syrup-Holding Tank

ABC Pharmaceutical Company	**CLEANING VALIDATION PROTOCOL** **Equipment Name**	
	Issued on **Date**	**Protocol Number** **CLVS-000**
	Location **Liquid Area** **Room No. 000**	

Equipment . . . . . **Equipment Name**

Model . . . . . **Model/Number**

Manufacturer . . . . . **Name and country**

Written by — **Signature & Date**

Validation Officer _____

Reviewed by — **Signature & Date**

QA Manager _____

Signature & Date

QC Manager _____

Signature & Date

Production Manager _____

Approved by — **Signature & Date**

Production Director _____

Authorized by — **Signature & Date**

QA Director _____

36.3.1 Objective

The objective of this protocol is to demonstrate that the cleaning procedure will successfully and consistently reduce the level of residues to a predetermined level of acceptability, for the six identical holding tanks in the syrup manufacturing area.

36.3.2 Scope

This protocol will cover the cleaning process of holding tanks 01, 02, 03, 04, 05, and 06, which are used for holding syrup products.

36.3.3 Validation Approach

This protocol covers the cleaning validation of holding tanks 01, 02, 03, 04, 05, and 06 for the syrup products. Since the same products are stored in the holding tanks, the same worst-case scenario would be applied for these identical tanks. Based on their equivalency, only one of these tanks would be used for cleaning validation purposes.

Table 36.3.1 lists the worst-case products for the above-mentioned holding tanks.

36.3.4 Responsibility

The following personnel are responsible for the execution of this protocol:

Cleaning validation officer/production officer/QA inspector/machine operator; for details, please refer to Attachment II.

36.3.5 Procedure

Three consecutive batches of products mentioned in Table 36.3.1 are taken into account to validate the corresponding cleaning procedures for the tanks mentioned above. The batches may be held in any one of the six tanks.

TABLE 36.3.1

Worst Case for Holding Tanks

Products	Justification for Worst Case
Multivitamins syrup	Less solubility (7), least soluble (three actives)
Promethazine HCl	High toxicity level (LD_{50} 255 mg/kg oral rat)
Paracetamol syrup	Maximum daily dosage (4.0 g/day)

36.3.6 Description of the Cleaning Process

Holding tanks 01–06 are cleaned by the CIP system as per SOP No. ABC-001.

36.3.6.1 Procedure

1. Ensure that there is no product in the intended tank for CIP
2. Connect the CIP flexible hose to the manufacturing tank and keep the valve in open position (Figure 36.3.1). Remove the sampling point before starting and keep a blind instead
3. From the control view computer, go to the menu of CIP/SIP and then select the intended CIP to be carried out
4. From the screen that will appear, select check boxes that are suitable for the product
   - Pre-rinse, caustic rinse is suitable for syrups and drops and other CIPs
   - Pre-rinse, acid rinse is suitable for suspensions
5. Click on "Start" and this will start CIP step by step as selected
6. When it is finished, it means that it is completed correctly and the tank is ready for production
7. Check the tank visually and then remove the flexible hose and refix the sample point
8. Make entries in the logbook

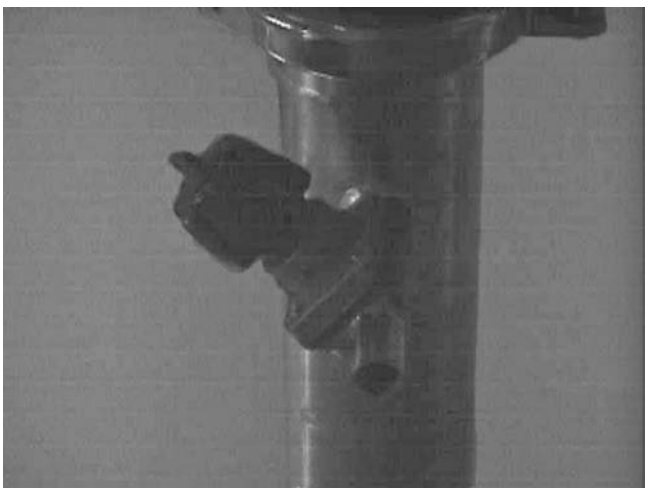


FIGURE 36.3.1
Valve of the syrup-holding tank.

36.3.7 Identification of Critical Parameters

The critical parameters should be monitored by the online monitoring system as stated in Table 36.3.2.

36.3.8 Description of the Sampling Process

36.3.8.1 Sampling Technique

The following sampling technique is used to take samples from syrup-holding tanks 01, 02, 03, 04, 05, and 06.

36.3.8.2 Sampling Precautions

Before taking the sample, wear

i. Hand gloves
ii. Face mask

36.3.8.3 Rinse Sample

The rinse sampling technique is used to take samples from syrup-holding tanks 01, 02, 03, 04, 05, and 06 (Figure 36.3.2). After the completion ofthe CIP cycle holding tank, take the rinse sample from the CIP return loop sampling point (Table 36.3.3).

36.3.8.4 Handling of Sample

Samples should be kept in the refrigerator, if not testing immediately.

Analyze the samples within 2 h after collection for pH, conductivity, and TOC.

HPLC analysis (MAC) and bio-burden should be performed within 24 h.

TABLE 36.3.2

Critical Parameters

Parameters	Specification	Actual Reading
Conductivity	Less than 5.0 µs/cm	
Temperature	60°C	
Water flood volume	1000 L/h	
Caustic NaOH	48%	
Phosphoric acid	(88%)	

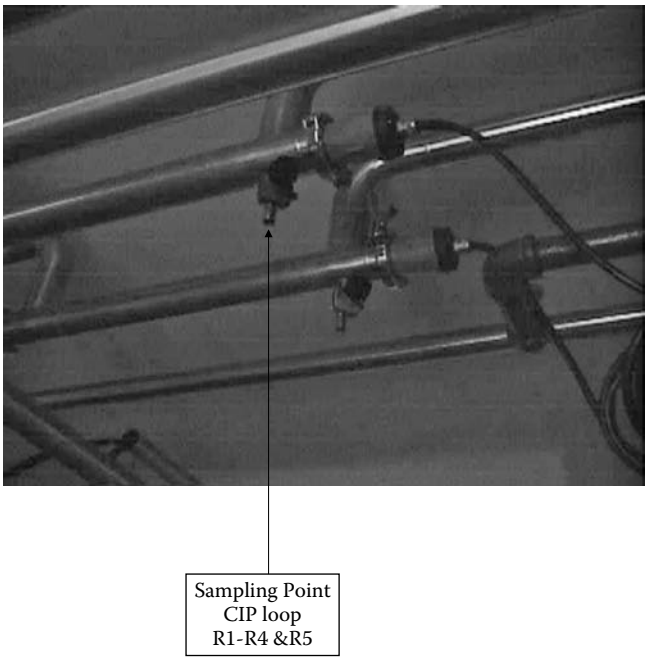


FIGURE 36.3.2
CIP loop of syrup-holding tank.

36.3.9 Test Functions

36.3.9.1 Visual Inspection

Inspection of holding tanks 01, 02, 03, 04, 05, and 06 should be performed visually. The tanks should be clean and free from any traces of residue.

For detailed information about sample ID, volume, testing specification, and testing method, see the sampling and testing plan in Table 36.3.3.

TABLE 36.3.3

Sampling and Testing Plan for Rinse Samples

S. No.	Sample Identification	Test	Sample Volume	Sampling Bottle	Testing Specifications	Testing Method/ Procedure No.
1	R1	pH	100 mL	Clean bottle	5–7 pH unit	STM-ABC-0001
2	R2	Conductivity	100 mL	Clean bottle	NMT 5.0 µs/cm	STM-ABC-0002
3	R3	TOC	100 mL	Clean bottle	NMT 500 ppb	SOP-ABC-003
4	R4	MAC	100 mL	Clean bottle	NMT MAC	Validated HPLC method
5	R5	Bio-burden	100 mL	Sterilized bottle	NMT 10 cfu/100 mL	STM-ABC-0003

36.3.10 Verification of Documents

i. Verify the syrup-holding tanks cleaning procedure.
ii. Verify the syrup-holding tanks cleaning logbook records.
iii. Verify the staff training record (refer to Attachment III).

36.3.11 Documentation

i. All analysis results are recorded in the analysis logbook.
ii. Printouts and chromatograms are attached to the validation report and a copy of that is also attached to the analytical logbook.
iii. All analysis and data should be verified by the second analyst.
iv. All training records are checked by the cleaning validation officer.
v. The final report for cleaning validation should be prepared by the cleaning validation officer.

36.3.12 Acceptance Criteria

a. *Visual inspection:* The visible internal equipment surfaces and all critical and difficult-to-clean parts are optically free from residue, and the color of the final rinse water is compared with DIW.
b. *pH determination:* The pH value of the rinse should be in between 5 and 7 and is comparable to DIW pH value.
c. *Conductivity:* The conductivity of the rinse should not be more than the conductivity of the blank DIW sample kept under the same conditions.
d. *Total organic carbon:* The TOC of the final rinse should be comparable to the blank DIW sample kept under the same conditions (DIW TOC limit is NMT 500 ppb).
e. *Maximum allowable carryover:* The active ingredient in the final rinse is either not detected or equal to or less than the MAC (calculated theoretically for product).

   Based on the solubility and maximum daily dose matrix, the MAC is calculated for each product. The MAC is calculated as follows:

$$\text{MAC} = \frac{\text{TD} \times \text{BS} \times \text{SF}}{\text{LDD}},$$

   where MAC is the maximum allowable carryover, TD is a single therapeutic dose, BS is the batch size of the next product to be manufactured in the same equipment, SF is the safety factor, and LDD is the largest daily dose of the next product to be manufactured in the same equipment.

The calculated value is the maximum amount of active ingredient of a certain product that is allowed to be carried over to the next batch.

f. *Bio-burden:* The bio-burden should not be more than 10 cfu/100 mL for the rinses.

36.3.13 List of Attachments

Attachment I	Description of equipment and product
Attachment II	Cleaning/testing responsibilities
Attachment III	Training record verification
Attachment IV	Rinse analysis results

Attachment I

Description of Equipment and Product

Equipment Name: _____

Serial No.: _____

Capacity: _____

Location: _____

Room No.: _____

Previous Product: _____

Batch No. of Previous Product: _____

Manufacturing Date: _____

Active Ingredient: _____

Therapeutic Group: _____

Cleaning Date: _____

Cleaning SOP No.: _____ Revision No.: _____

Sampling Technique: _____

Cleaning Sample Analysis Date/Time: _____ Result: _____

Test Method Reference: _____ Reference Analytical Logbook: _____

Limit of Detection: _____ Safety Factor: _____

Next Product to Be Manufactured in the Same Equipment: _____

Performed by: _____ Date: _____

Checked by: _____ Date: _____

Attachment II

Cleaning/Testing Responsibilities

Cleaning/Testing	Done By	Recorded On	Checked By
Equipment cleaning	Machine operator	Equipment usage/ cleaning logbook	Production manager
Visual inspection	Cleaning validation officer	Analytical logbook	Manager QA
Rinse sample	Machine operator/cleaning validation officer	Sampling sheet	Manager QA
pH	Cleaning validation officer/QC analyst	Analytical logbook	QA/QC officer
Conductivity	Cleaning validation officer/QC analyst	Analytical logbook	QA/QC officer
TOC	Cleaning validation officer/QC analyst	Analytical logbook	QA/QC officer
MAC	Cleaning validation officer/QC analyst	Analytical logbook	QC officer
Bio-burden	Cleaning validation officer/microbiologist	Analytical logbook	Manager Microbiology QC Laboratory

TOC, total organic carbon; MAC, maximum allowable carryover.

Performed by: _____ Date: _____

Checked by: _____ Date: _____

Attachment III

Training Record Verification

The following staff were found trained on cleaning of equipment.

Using SOP No. ABC-003; Revision No.; Issued on; Date

Name: _____ ID No.: _____ Sign.: _____ Date: _____

Name: _____ ID No.: _____ Sign.: _____ Date: _____

Performed by: _____ Date: _____

Checked by: _____ Date: _____

Attachment IV

Rinse Analysis Results

Sampling ID	Blank DIW			Rinse Sample				
	pH	**Conductivity**	**TOC**	**Total Carryover HPLC Result**	**pH (Limit 5–7)**	**Conductivity NMT 5.0 µs/cm at 25°C**	**TOC NMT 500 ppb**	**Bio-Burden**
R1–R4								
R5								
HPLC chromatogram printouts should be attached to the analytical logbook.								

Performed by: _____ Date: _____

Checked by: _____ Date: _____

CLV-36.4

Protocol for Filling Station and Filter Assembly

Your Company's Logo

Your Company's Name

ABC Pharmaceutical Company	**CLEANING VALIDATION PROTOCOL** **Equipment Name**	
	Issued on: **Date**	**Protocol Number** **CLVL-000**
	Location **Filling Area**	

Equipment ..... **Filling line and filter assembly**

Model ..... **Model and make**

Manufacturer ..... **Company, Country**

Written by	**Signature & Date**
Validation Officer	_____
Reviewed by	**Signature & Date**
Manager QA	_____
Production Manager	**Signature & Date**
	_____
QC Manager	**Signature & Date**
	_____
Packaging Manager	**Signature & Date**
	_____
Authorized by	**Signature & Date**
QA Director	_____

Your Company's Logo Your Company's Name

36.4.1 Protocol for Filling Machine (Type A)

36.4.1.1 Objective

The objective of this protocol is to demonstrate that the cleaning procedure will successfully and consistently reduce the level of residues to a predetermined level of acceptability for the filling machine line 1 with the corresponding filtration assembly.

36.4.1.2 Scope

This protocol will cover cleaning of the ABC filling machine line 1 and for the filtration assemblies thereof for the syrup products.

36.4.1.3 Cleaning Validation Approach

A worst-case determination for the cleaning validation was done in the cleaning validation master plan. As per the product matrix in the VMP, the following worst-case products were selected to validate the cleaning procedure of the filling machine. The products are divided into various categories (groups), based on water solubility, maximum dosage, and batch size and toxicity factor. From each group one worst-case product should be analyzed for cleaning validation (Table 36.4.1.1).

Since all the products are manufactured in 7000-L batch size, including the three worst cases shown in Table 36.4.1.1, a worst case exclusively for maximum batch size is not deemed necessary.

36.4.1.4 Responsibilities

The following personnel are responsible for the execution of this protocol:

Validation officer/production officer/QA inspector and machine operator; for details, please refer to Attachment II.

36.4.1.5 Description of the Cleaning Process

Filling machine is cleaned manually as per SOP No. ABC-001.

TABLE 36.4.1.1

Worst Case for Filling Line 1 for Syrup Products

Products	Justification for Worst Case
Multivitamins syrup	Less solubility (7), least soluble (three vitamin APIs)
Promethazine syrup	High toxicity level (LD_{50} 255 mg/kg oral rat)
Paracetamol	Maximum daily dosage (4.0 g/day)

Your Company's Logo **Your Company's Name**

I. Filling machine (at the product changeover, weekend and after every 3 days, in the case of campaign filling and packaging operation)
   1. At the end of filling, close the product supply
   2. Request the production supervisor for CIP cleaning of the bulk transfer line and hopper through CIP request for syrups
   3. Dislodge the hose connecting the filling machine to the bulk storage tank and place the end of the hose in a vessel containing deionized water
   4. Pass the deionized water through the hose and pistons until clean water is obtained
   5. Disconnect all pistons, nozzles and pipe of the filling machine and of the filling tank, the gaskets and the connections, and clean them thoroughly with water. If required, use a brush and clean all the corners and crevices until no traces of the previous product are seen
   6. Finally rinse them with 70% ethanol
   7. Assemble the parts taken out for cleaning
   8. Clean the remaining parts of the filling machine including the machine base, conveyer belt, and the cabinet with a wet mop of deionized water until the whole area is optically clean

II. Filtration units (product changeover, weekend and after every 3 days in the case of campaign filling of the same product)
   Cleaning procedure for the filter:
   1. Dismantle the filter
   2. Clean the stainless steel part first with soap water and then with 70% ethanol
   3. Rinse the filter with deionized water until clean water is obtained. Ensure that there are no traces of the product
   4. If the filter is damaged, replace it with a new one
   5. Rinse with 70% ethanol

III. Filling tank (product changeover and weekend)
   1. Open the cover of the filling machine
   2. Disconnect the pipes and gaskets
   3. Clean the internal surface with a sponge of DIW until it is thoroughly clean
   4. Clean the pipes and gaskets with DIW until there is no residue left. Finally, clean with 70% ethanol
   5. Clean the outside of the tank with a sponge of DIW
   6. Spray 70% ethanol on the inside of the tank and on the external surface of the tank

36.4.1.6 Identification of Critical Parameters

The critical parameters are monitored as stated in Table 36.4.1.2.

Your Company's Logo

Your Company's Name

TABLE 36.4.1.2
Critical Parameters

Parameters	Specification	Actual Reading
Temperature	90°C	
Time		
Ethanol	70%	
Filters		

36.4.1.7 Description of the Sampling Process

36.4.1.7.1 Sampling Technique

The following sampling techniques are used to take samples from filling machine parts, filtration assembly, and filling tank.

a. Surface swabs (sterile cotton swabs wetted with DIW)
b. Water rinses (in clean bottle as listed below)

See Figures 36.4.1.1 through 36.4.1.3 for sampling locations.

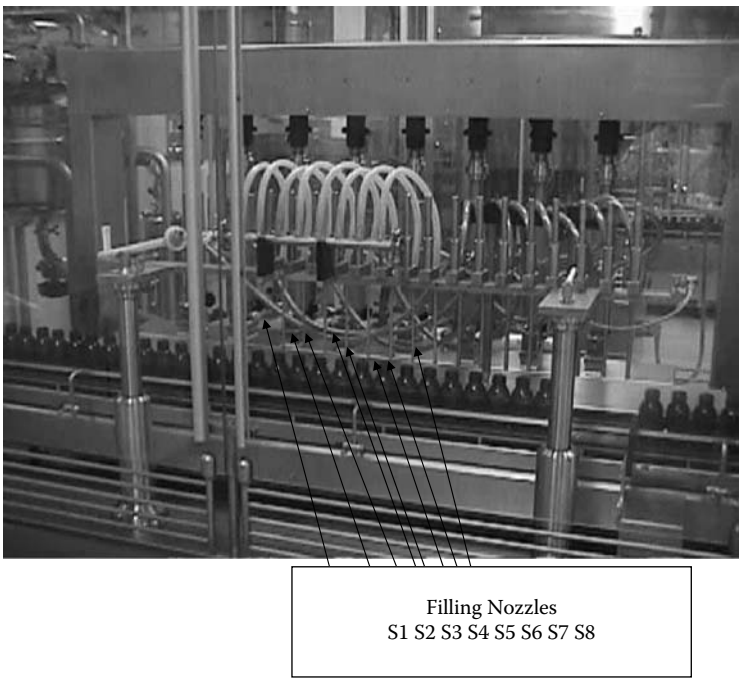


FIGURE 36.4.1.1
Filling nozzles sampling locations.

Your Company's Logo **Your Company's Name**

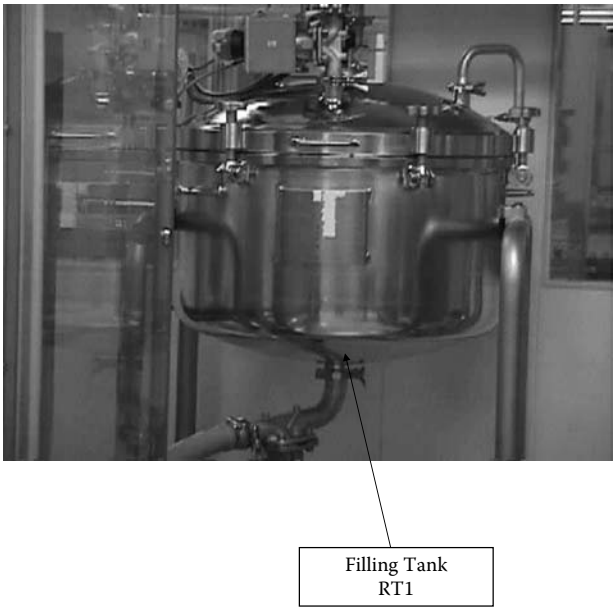


FIGURE 36.4.1.2
Filling tank sampling location.

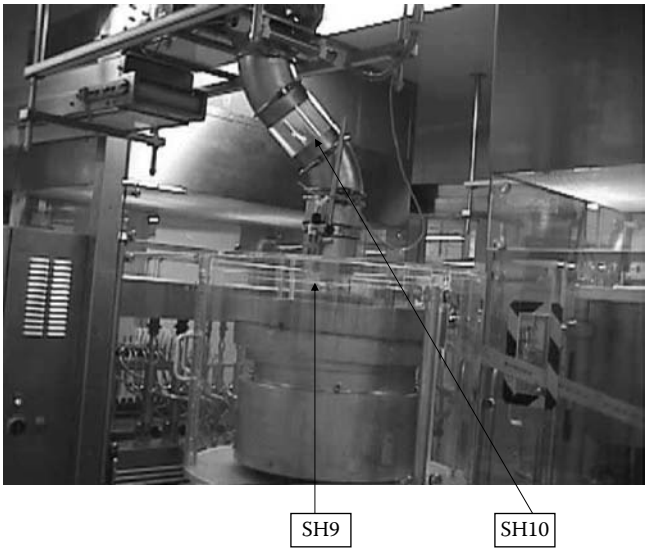


FIGURE 36.4.1.3
Hopper sampling locations.

Your Company's Logo **Your Company's Name**

36.4.1.7.2 Surface Swabs

36.4.1.7.2.1 Procedure for Sampling

Sampling should be performed as per SOP No. ABC-002; the cleaning validation officer is responsible for taking the swab sample. Samples of the internal surfaces are taken by moistening the swab (ready-made sterile cotton swab) with a suitable solvent (DIW). Sample a 25-cm^2 area and place the swab in a test tube containing 10 mL of solvent (DIW). Swab samples from each part of filling machine are collected as per Tables 36.4.1.3 and 36.4.1.4.

36.4.1.7.2.2 Sampling Precautions

Before taking the sample, wear

i. Hand gloves
ii. Face mask

36.4.1.7.2.3 Rinse Sample

The rinse sampling technique is used to take samples from filling machine parts. After the completion of cleaning, take rinse sample from filling machine parts as per the sampling and testing plan for rinses.

36.4.1.7.2.4 Handling of Samples

Samples should be kept in the refrigerator, if not testing immediately.

TABLE 36.4.1.3

Sampling and Testing Plan for Rinses

S. No.	Sample Identification	Test	Sample Volume (mL)	Sampling Bottle	Testing Specifications	Testing Method/ Procedure No.
1	*RN1-RN8-RF1 *RH1 and *RT1	pH	100	Clean bottle	5–7 pH unit	STM-PL-001
2	RN1-RN8-RF1 RH1 and RT1	Conductivity	100	Clean bottle	NMT 5.0 µs/cm	
3	RN1-RN8-RF1 RH1 and RT1	TOC	100	Clean bottle	NMT 500 ppb	SOP-ABC-005
4	RN1-RN8-RF1 RH1 and RT1	MAC	100	Clean bottle	NMT MAC	Validated HPLC method
5	RN1-RN8-RF1 RH1 and RT1	Bio-burden	100	Sterilized bottle	NMT 10 cfu/100 mL	STM-MC-001
6	RND1-RND8 RHD1 and RTD1	Detergent	100	Clean bottle	No foam detected	—

*RN: rinse from nozzle; *RH: rinse from hose; *RT: rinse from tank; *RHD, RND, and RTD: sample for detergent testing; *RF: rinse from filters.

Your Company's Logo **Your Company's Name**

TABLE 36.4.1.4

Sampling and Testing Plan for Swabs

S. No.	Sampling Location	Sample Identification	Test	Specifications
1	Filling nozzles	SN1	MAC by the suitable validated HPLC method	Less than or equal to the limit of detection
2		SN2		
3		SN3		
4		SN4		
5		SN5		
6		SN6		
7		SN7		
8		SN8		
9	Hopper	SH9		
10		SH10		
11	Filter	SF11		

Analyze the samples within 2 h after collection for pH, conductivity, and TOC and detergent detection.

HPLC analysis (MAC) should be performed within 24 h.

36.4.1.8 Test Functions

36.4.1.8.1 Visual Inspection

Inspection of filling machine parts, filters, and filling tank is performed visually.

36.4.1.9 Verification of Documents

i. Verify the filling machine dosing cleaning procedure.
ii. Verify the dosing cleaning logbook records.
iii. Verify the staff training record (refer to Attachment III).

36.4.1.10 Documentation

i. All analysis results are recorded in the analysis logbook.
ii. Printouts and chromatograms are attached to the validation report and a copy of that is also attached to the analytical logbook.
iii. All analysis and data should be verified by the second analyst.
iv. All training records are checked by the cleaning validation officer.
v. Final report for cleaning validation should be prepared by the cleaning validation officer.

Your Company's Logo Your Company's Name

36.4.1.11 Acceptance Criteria

a. *Visual inspection:* The visible internal equipment surfaces and all critical and difficult-to-clean parts are optically free from residue, and the color of the final rinse water is comparable to DIW.
b. *pH determination:* The pH value of the rinse should be in between 5 and 7 and comparable to DIW pH value.
c. *Conductivity:* The conductivity of the rinse should not be more than the conductivity of the blank DIW sample kept under the same conditions.
d. *Total organic carbon:* The TOC of the final rinse should be comparable to blank DIW sample kept under the same conditions (DIW TOC limit is NMT 500 ppb).
e. *Detergent detection:* No foam is detected on the top of the rinse sample after testing.
f. *Maximum allowable carryover:* The active ingredient in the final rinse is either not detected or equal to or less than the MAC (calculated theoretically for product).

   Based on solubility, toxicity, and maximum daily dose matrix, the MAC is calculated for each product. The MAC is calculated as follows:

$$\text{MAC} = \frac{\text{TD} \times \text{BS} \times \text{SF}}{\text{LDD}},$$

   where MAC is the maximum allowable carryover, TD is a single therapeutic dose, BS is the batch size of the next product to be manufactured in the same equipment, SF is the safety factor, and LDD is the largest daily dose of the next product to be manufactured in the same equipment.

   The calculated value is the maximum amount of active ingredient of a certain product that is allowed to be carried over to the next batch.
g. *Bio-burden:* The bio-burden should not be more than 10 cfu/100 mL for the rinses.

36.4.1.12 List of Attachments

Attachment I	Description of equipment and product
Attachment II	Cleaning/testing responsibilities
Attachment III	Sampling technique
Attachment IV	Rinse analysis results
Attachment V	Swab analysis results

Your Company's Logo **Your Company's Name**

Attachment I

Description of Equipment and Product

Equipment Name: _____

Serial No.: _____

Capacity: _____

Location: _____

Previous Product: _____

Batch No. of Previous Product: _____

Manufacturing Date: _____

Active Ingredient: _____

Therapeutic Group: _____

Cleaning Date: _____

Cleaning SOP No.: _____ Revision No.: _____

Sampling Technique: _____

Cleaning Sample Analysis Date/Time: _____ Result: _____

Test Method Reference: _____ Reference Analytical Logbook: _____

Limit of Detection: _____ Safety Factor: _____

Next Product to Be Manufactured in the Same Equipment: _____

Performed by: _____ Date: _____

Checked by: _____ Date: _____

Your Company's Logo **Your Company's Name**

Attachment II

Cleaning/Testing Responsibilities

Cleaning/Testing	Done By	Recorded On	Checked By
Equipment cleaning	Machine operator	Equipment usage/ cleaning logbook	Production manager
Visual inspection	Cleaning validation officer	Analytical logbook	Manager QA
Rinse sample	Machine operator/validation officer	Sampling sheet	Manager QA
pH/detergent	Validation officer/QC analyst	Analytical logbook	Validation/QC officer
Conductivity	Validation officer/QC analyst	Analytical logbook	Validation/QC officer
TOC	Validation officer/QC analyst	Analytical logbook	Validation/QC officer
MAC	Validation officer/QC analyst	Analytical logbook	QC analyst
Bio-burden	Validation officer/microbiologist	Analytical logbook	Manager QC, microbiology

TOC, total organic carbon; MAC, maximum allowable carryover.

Performed by: _____ Date: _____

Checked by: _____ Date: _____

Your Company's Logo **Your Company's Name**

Attachment III

Training Record Verification

The following staff were found trained on cleaning of equipment.

Using SOP No. ABC-005; Revision No.; Issued on; Date

Name: _____ ID No.: _____ Sign.: _____ Date: _____

Name: _____ ID No.: _____ Sign.: _____ Date: _____

Performed by: _____ Date: _____

Checked by: _____ Date: _____

Your Company's Logo **Your Company's Name**

Attachment IV

Rinse Analysis Results

Sampling ID	Blank DIW			Rinse Sample					
	PH	Conductivity	TOC	Total carryover HPLC Result	pH (Limit 5–7)	Conductivity NMT 5.0 µs/cm at 25°C	TOC NMT 500 ppb	Detergent Determination	Bio-Burden
RN1									
RN2									
RN3									
RN4									
RN5									
RN6									
RN7									
RN8									
RH1									
RT1 RN1									
RND1–RND8 RHD1 and RTD1									
HPLC chromatogram printouts should be attached to the analytical logbook.									

Performed by: _____ Date: _____

Checked by: _____ Date: _____

Your Company's Logo **Your Company's Name**

Attachment V

Swab Analysis Results

Sampling Location/ID	Visual Inspection	Carryover HPLC Result per 25 cm^2	25 cm^2 × Surface Area (Total Carryover)
S1			
S2			
S3			
S4			
S5			
S6			
S7			
S8			
S9			
S10			
S11			

Performed by: _____ Date: _____

Checked by: _____ Date: _____

Your Company's Logo

Your Company's Name

36.4.2 Protocol for Filling Station (Type B)

ABC Pharmaceutical Company	**CLEANING VALIDATION PROTOCOL** **Equipment Name**	
	Issued on **Date**	**Protocol Number** **CLVL-000**
	Location **Filling Area**	

Equipment ..... **Filling line and Filter Assembly**

Model ..... **Model and make**

Manufacturer ..... **Company, Country**

36.4.2.1 Objective

The objective of this protocol is to demonstrate that the cleaning procedure will successfully and consistently reduce the level of residues to a predetermined level of acceptability for the filling machine line 4 with the corresponding filtration assembly.

36.4.2.2 Scope

This protocol will cover the cleaning process of the filling machine line 2 and for the filtration assembly and thereof for the suspension products.

36.4.2.3 Validation Approach

This protocol covers the cleaning validation of manufacturing vessel No. MF-001 for the suspension products. Since the same products are filled in the filling line, the same worst-case scenario would be applied for this filling line.

As per the products matrix in the VMP, all products are divided into various categories (groups), based on water solubility, toxicity, maximum daily usage, and the batch size. From each group, one worst-case product should be analyzed for cleaning validation (Table 36.4.2.1).

Since all the products are manufactured with the same batch size, that is, 7500 L, a worst-case product for the largest batch size cleaning does not seem necessary for this filling line.

Your Company's Logo

Your Company's Name

TABLE 36.4.2.1

Worst Case for Filling Line 1

Products	Justification for Worst Case
Al/Mg hydroxide suspension	Less solubility (7), least soluble Al hydroxide Mg hydroxide Simethicone
Profinal suspension	High toxicity level (LD_{50} 636 mg/kg oral rat)
Kaolin suspension	Maximum daily dosage (5.4 g/day)

36.4.2.4 Responsibilities

The following personnel are responsible for the execution of this protocol:

Cleaning validation officer/production officer/QA inspector/machine operator. For details, please refer to Attachment II.

36.4.2.5 Description of the Cleaning Process

The filling machine should be cleaned manually as per SOP No. ABC-002.

I. Filling machine (at the product changeover, weekend and after every 3 days in the case of campaign filling and packaging operation)
   1. At the end of filling, close the product supply.
   2. Request the production supervisor for CIP cleaning of the bulk transfer line and hopper through CIP request for syrups.
   3. Dislodge the hose connecting the filling machine to the bulk storage tank and place the end of the hose in a vessel containing deionized water.
   4. Pass the deionized water through the hose and pistons until clean water is obtained.
   5. Disconnect all pistons, nozzles and pipe of filling machine and of the filling tank, the gaskets and the connections and clean them thoroughly with water. If required, use a brush and clean all the corners and crevices until no traces of the previous product are seen.
   6. Finally, rinse them with 70% ethanol.
   7. Assemble the parts taken out for cleaning.
   8. Clean the remaining parts of the filling machine including the machine base, conveyer belt, and the cabinet with a wet mop of deionized water until the whole area is optically clean.

II. Filtration units (product changeover, weekend and after every 3 days in the case of campaign filling of the same product)

Cleaning procedure for the filter:

1. Dismantle the filter.
2. Clean the stainless steel part first with soap water and then with 70% ethanol.
3. Rinse the filter with deionized water until clean water is obtained. Ensure that there are no traces of the product.
4. If the filter is damaged, replace with a new one.
5. Then rinse with 70% ethanol.

III. Filling tank (product changeover and weekend)

1. Open the cover of the filling machine.
2. Disconnect the pipes and gaskets.
3. Clean the internal surface with a sponge of DIW until thoroughly clean.
4. Clean the pipes and gaskets with DIW until there is no residue left. Finally, clean with 70% ethanol.
5. Clean the outside of the tank with a sponge of DIW.
6. Spray 70% ethanol on the inside of the tank and on the external surface of the tank.

36.4.2.6 Identification of Critical Parameters

The critical parameters should be monitored as stated in Table 36.4.2.2.

36.4.2.7 Description of the Sampling Process

A. *Sampling Technique:* The following sampling techniques are used to take samples from filling machine parts, filtration assembly, and filling tank.
   a. Surface swabs (sterile cotton swabs wetted with WFI)
   b. Water rinses (in clean bottle as listed below)

TABLE 36.4.2.2

Critical Parameters

Parameters	Specification	Actual Reading
Temperature	90°C	
Time		
Purified water volume		
Ethanol	70%	
Detergent concentration		

Your Company's Logo **Your Company's Name**

36.4.2.7.1 Surface Swabs

36.4.2.7.1.1 Procedure for Swab Sampling

Sampling should be performed as per SOP No. ABC-003; the cleaning validation officer is responsible for taking the swab sample Samples of the internal surfaces are taken by moistening the swab (ready-made sterile cotton swab) with a suitable solvent (DIW) Sample a 25-cm^2 area and place the swab in a test tube containing 10 mL of solvent (DIW) Swab sample should be taken as per the sampling and testing plan

36.4.2.7.1.2 Sampling Precautions

Before taking the sample, wear

i. Hand gloves
ii. Face mask

36.4.2.7.1.3 Rinse Sample

The rinse sampling technique is used for taking samples from filling machine parts and filtration assembly. After cleaning, take the rinse sample as per the sampling and testing plan (Tables 36.4.2.3 and 36.4.2.4).

36.4.2.7.1.4 Handling of Samples

Samples should be kept in the refrigerator, if not testing immediately.

Analyze the samples within 2 h after collection for pH, conductivity, and TOC and detergent detection.

TABLE 36.4.2.3

Sampling and Testing Plan for Rinses

S. No.	Sample Identification	Test	Sample Volume (mL)	Sampling Bottle	Testing Specifications	Testing Method/ Procedure No.
1	*RN1–RN8 *RH1 and *RT1, RF1	pH	100	Clean bottle	5–7 pH unit	STM-PL-001
2	RN1–RN8 RH1 and RT1, RF1	Conductivity	100	Clean bottle	NMT 5.0 µs/cm	
3	RN1–RN8 RH1 and RT1, RF1	TOC	100	Clean bottle	NMT 500 ppb	SOP-QC-001
4	RN1–RN8 RH1 and RT1, RF1	MAC	100	Clean bottle	NMT MAC	Validated HPLC method
5	RN1–RN8 RH1 and RT1, RF1	Bio-burden	100	Sterilized bottle	NMT 10 cfu/100 mL	STM-MC-001
6	RND1–RND8 RHD1 and RTD1	Detergent	100	Clean bottle	No foam detected	—

*RN: rinse from nozzle; *RH: rinse from hose; *RT: rinse from tank; *RHD, RND, and RTD: sample for detergent testing; *RF: rinse from filter.

Your Company's Logo **Your Company's Name**

TABLE 36.4.2.4

Sampling and Testing Plan for Swabs

S. No.	Sampling Location	Sample Identification	Test	Specifications
1	Filling nozzles	SN1	MAC by a suitable validated HPLC method	Less than or equal to the limit of detection
2		SN2		
3		SN3		
4		SN4		
5		SN5		
6		SN6		
7		SN7		
8		SN8		
9	Hopper	SH9		
10		SH10		
11	Filter	SF11		

HPLC analysis (MAC) and bio-burden should be performed within 24 h.

36.4.2.8 Test Functions

36.4.2.8.1 Visual Inspection

Inspection of filling machine parts, filtration assembly, and filling tank is performed visually.

36.4.2.9 Verification of Documents

i. Verify the Bausch and Strobel dosing cleaning procedure.
ii. Verify the Bausch and Strobel cleaning logbook records.
iii. Verify the staff training record (refer to Attachment III).

36.4.2.10 Documentation

i. All analysis results are recorded in the analysis logbook.
ii. Printouts and chromatograms are attached to the validation report and a copy of that is also attached to the analytical logbook.
iii. All analysis and data should be verified by the second analyst.
iv. All training records are checked by the cleaning validation officer.
v. The final report for cleaning validation should be prepared by the cleaning validation officer.

Your Company's Logo Your Company's Name

36.4.2.11 Acceptance Criteria

a. *Visual inspection:* The visible internal equipment surfaces and all critical and difficult-to-clean parts are optically free from residue, and the color of the final rinse water is comparable to DIW.

b. *pH determination:* The pH value of the rinse should be in between 5 and 7 and comparable to DIW pH value.

c. *Conductivity:* The conductivity of the rinse should not be more than the conductivity of the blank DIW sample kept under the same conditions.

d. *Total organic carbon:* The TOC of the final rinse should be comparable to the blank DIW sample kept under the same conditions (DIW TOC limit is NMT 500 ppb)

e. *Detergent detection:* No foam is detected on top of the rinse sample after testing.

f. *Maximum allowable carryover:* The active ingredient in the final rinse is either not detected or equal to or less than the MAC (calculated theoretically for product).

Based on solubility and maximum daily dose matrix, the MAC will be calculated for each product. The MAC is calculated as follows:

$$\text{MAC} = \frac{\text{TD} \times \text{BS} \times \text{SF}}{\text{LDD}},$$

where MAC is the maximum allowable carryover, TD is a single therapeutic dose, BS is the batch size of the next product to be manufactured in the same equipment, SF is the safety factor, and LDD is the largest daily dose of the next product to be manufactured in the same equipment. The calculated value is the maximum amount of active ingredient of certain product, which is allowed to be carried over to the next batch.

g. *Bio-burden:* The bio-burden should not be more than 10 cfu/100 mL for the rinses.

36.4.1.12 List of Attachments

Attachment I	Description of equipment and product
Attachment II	Cleaning/testing responsibilities
Attachment III	Training record verification
Attachment IV	Rinse analysis results
Attachment V	Swab analysis results

Your Company's Logo **Your Company's Name**

Attachment I

Description of Equipment and Product

Equipment Name: _____

Serial No.: _____

Capacity: _____

Location: _____

Previous Product: _____

Batch No. of Previous Product: _____

Manufacturing Date: _____

Active Ingredient: _____

Therapeutic Group: _____

Cleaning Date: _____

Cleaning SOP No.: _____ Revision No.: _____

Sampling Technique: _____

Cleaning Sample Analysis Date/Time _____ Assay Result: _____

Test Method Reference: _____ Reference Analytical Logbook: _____

Limit of Detection: _____ Safety Factor: _____

Next Product to Be Manufactured in the Same Equipment: _____

Performed by: _____ Date: _____

Checked by: _____ Date: _____

Your Company's Logo **Your Company's Name**

Attachment II

Cleaning/Testing Responsibilities

Cleaning/Testing	Done By	Recorded On	Checked By
Equipment cleaning	Machine operator	Equipment usage/ cleaning logbook	Production manager
Visual inspection	Cleaning validation officer	Analytical logbook	Manager QA
Rinse sample	Machine operator/cleaning validation officer	Sampling sheet	Manager QA
pH/detergent	Cleaning validation officer/QC analyst	Analytical logbook	QA/QC officer
Conductivity	Cleaning validation officer/QC analyst	Analytical logbook	QA/QC officer
TOC	Cleaning validation officer/QC analyst	Analytical logbook	QA/QC officer
MAC	Cleaning validation officer/QC analyst	Analytical logbook	QC analyst
Bio-burden	Cleaning validation officer/microbiologist	Analytical logbook	Manager QC, microbiology-section

TOC, total organic carbon; MAC, maximum allowable carryover.

Performed by: _____ Date: _____

Checked by: _____ Date: _____

Your Company's Logo **Your Company's Name**

Attachment III

Training Record Verification

The following staff were found trained on cleaning of equipment.

Using SOP No. ABC-004; Revision No.; Issued on; Date

Name: _____ ID No.: _____ Sign.: _____ Date: _____

Name: _____ ID No.: _____ Sign.: _____ Date: _____

Performed by: _____ Date: _____

Checked by: _____ Date: _____

Your Company's Logo **Your Company's Name**

Attachment IV

Rinse Analysis Results

Sampling ID	Blank DIW			Rinse Sample					
	pH	Conduc-tivity	TOC	Total Carryover HPLC Result	pH (Limit 5–7)	Conductivity NMT 5.0 µs/ cm at 25°C	TOC NMT 500 ppb	Detergent Determination	Bio-Burden
RN1									
RN2									
RN3									
RN4									
RN5									
RN6									
RN7									
RN8									
RH1									
RT1 RF1									
RND1–RND8 RHD1 and RTD1									
HPLC chromatogram printouts should be attached to the analytical logbook.									

Performed by: _____ Date: _____

Checked by: _____ Date: _____

Your Company's Logo **Your Company's Name**

Attachment V

Swab Analysis Results

Sampling Location/ID	Visual Inspection	Carryover HPLC Result per 25 cm^2	25 cm^2 × Surface Area (Total Carryover)
S1			
S2			
S3			
S4			
S5			
S6			
S7			
S8			
S9			
S10			

Performed by: _____ Date: _____

Checked by: _____ Date: _____

Your Company's Logo **Your Company's Name**

36.4.3 Protocol for Filling Station (Type C)

ABC Pharmaceutical Company	**CLEANING VALIDATION PROTOCOL** **Equipment Name**	
	Issued on **Date**	**Protocol Number** **CLVL-000**
	Location **Filling Area**	

Equipment ..... **Filling line and Filter Assembly**

Model ..... **Model and make**

Manufacturer ..... **Company, Country**

Your Company's Logo **Your Company's Name**

Only the testing and sampling plan is given here since all other procedures remains the same as for the previous two types of filling stations. See Tables 36.4.3.1 and 36.4.3.2 for rinses and swabs samples details. For swab sample locations, see Figures 36.4.3.1 and 36.4.3.2.

36.4.3.1 Test Functions

36.4.3.1.1 Visual Inspection

Inspection of filling machine parts, filtration assembly, and filling tank is performed visually.

TABLE 36.4.3.1

Sampling and Testing Plan for Rinses

S. No.	Sample Identification	Test	Sample Volume (mL)	Sampling Bottle	Testing Specifications	Testing Method/ Procedure No.
1	*RN1–RF1 *RH1 and *RT1	pH	100	Clean bottle	5–7 pH unit	STM-ABC-001
2	RN1–RF1 RH1 and RT1	Conductivity	100	Clean bottle	NMT 5.0 µs/cm	
3	RN1–RF1 RH1 and RT1	TOC	100	Clean bottle	NMT 500 ppb	SOP-ABC-005
4	RN1–RF1 RH1 and RT1	MAC	100	Clean bottle	NMT MAC	Validated HPLC method
5	RN1–RF1 RH1 and RT1	Bio-burden	100	Sterilized bottle	NMT 10 cfu/100 mL	STM-MC-001
6	RND1 RHD1 and RTD1	Detergent	100	Clean bottle	No foam detected	—

*RN: rinse from nozzle; *RH: rinse from hose; *RT: rinse from tank; *RHD, RND, and RTD: rinse samples for detergent testing; *RF: rinse sample from filter.

TABLE 36.4.3.2

Sampling and Testing Plan for Swabs

S. No.	Sampling Location	Sample Identification	Test	Specifications
1	Filling nozzles	S1	MAC by a suitable validated HPLC method	Less than or equal to the limit of detection
2	Hopper	S2		
3		S3		

Your Company's Logo **Your Company's Name**

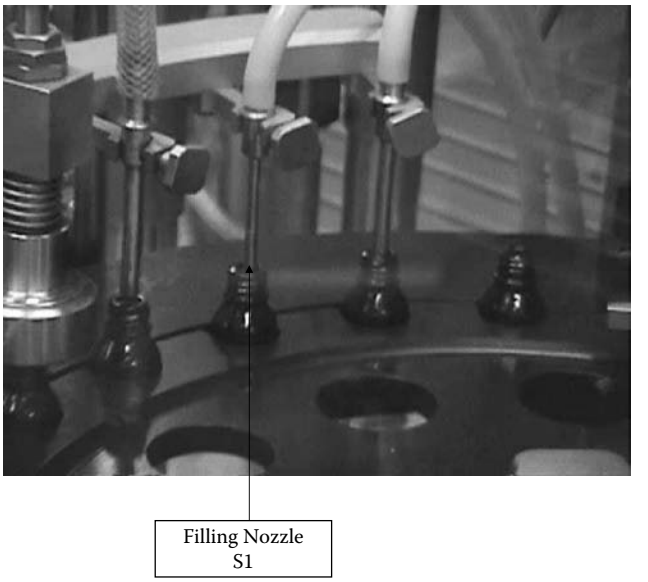


FIGURE 36.4.3.1
Filling nozzle machine type C.

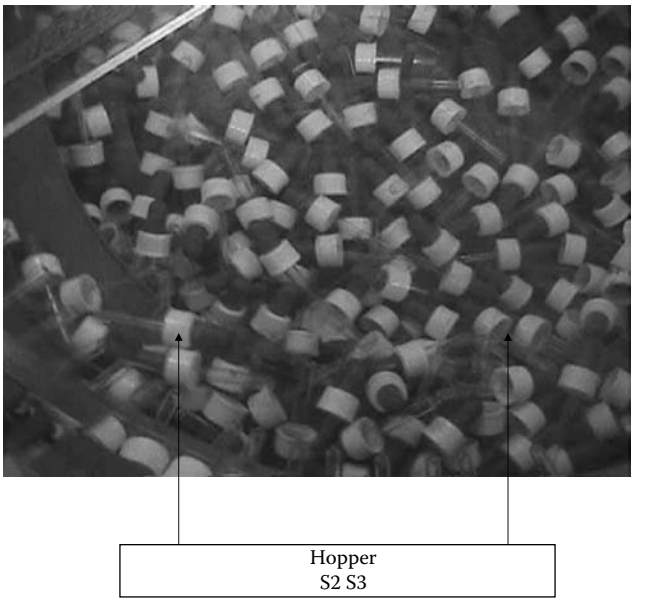


FIGURE 36.4.3.2
Dropper hopper.

Your Company's Logo Your Company's Name

36.4.3.1.2 Verification of Documents

i. Verify the dosing cleaning procedure
ii. Verify the dosing cleaning logbook records
iii. Verify the staff training record (refer to Attachment III)

36.4.3.2 Documentation

i. All analysis results are recorded in the analysis logbook.
ii. Printouts and chromatograms are attached to the validation report and a copy of that is also attached to the analytical logbook.
iii. All analysis and data should be verified by the second analyst.
iv. All training records are checked by the cleaning validation officer.
v. The final report for cleaning validation should be prepared by the cleaning validation officer.

36.4.3.3 Acceptance Criteria

a. *Visual inspection:* The visible internal equipment surfaces and all critical and difficult-to-clean parts are optically free from residue, and the color of the final rinse water is comparable to DIW.
b. *pH determination:* The pH value of the rinse should be in between 5 and 7 and comparable to DIW pH value.
c. *Conductivity:* The conductivity of the rinse should not be more than the conductivity of the blank DIW sample kept under the same conditions.
d. *Total organic carbon:* The TOC of the final rinse should be comparable to the blank DIW sample kept under the same conditions (DIW TOC limit is NMT 500 ppb).
e. *Detergent detection:* No foam is detected on top of the rinse sample after testing.
f. *Maximum allowable carryover:* The active ingredient in the final rinse is either not detected or equal to or less than the MAC (calculated theoretically for product).

Based on solubility and maximum daily dose matrix, the MAC is calculated for each product. The MAC is calculated as follows:

$$\text{MAC} = \frac{\text{TD} \times \text{BS} \times \text{SF}}{\text{LDD}},$$

where MAC is the maximum allowable carryover, TD is a single therapeutic dose, BS is the batch size of the next product to be manufactured in the same equipment, SF is the safety factor, and LDD is the largest daily dose of the next product to be manufactured in the same equipment.

Your Company's Logo **Your Company's Name**

The calculated value is the maximum amount of active ingredient of a certain product that is allowed to be carried over to the next batch.

g. *Bio-burden:* The bio-burden should not be more than 10 cfu/100 mL for the rinses

36.4.3.4 List of Attachments

Attachment I	Description of equipment and product
Attachment II	Cleaning/testing responsibilities
Attachment III	Training record verification
Attachment IV	Rinse analysis results
Attachment V	Swab analysis results

Your Company's Logo **Your Company's Name**

Attachment I

Description of Equipment and Product

Equipment Name: _____

Serial No.: _____

Capacity: _____

Location: _____

Previous Product: _____

Batch No. of Previous Product: _____

Manufacturing Date: _____

Active Ingredient: _____

Therapeutic Group: _____

Cleaning Date: _____

Cleaning SOP No.: _____ Revision No.: _____

Sampling Technique: _____

Cleaning Sample Analysis Date/Time: _____ Result: _____

Test Method Reference: _____ Reference Analytical Logbook: _____

Limit of Detection: _____ Safety Factor: _____

Next Product to Be Manufactured in the Same Equipment: _____

Performed by: _____ Date: _____

Checked by: _____ Date: _____

Your Company's Logo **Your Company's Name**

Attachment II

Cleaning/Testing Responsibilities

Cleaning/Testing	Done By	Recorded On	Checked By
Equipment cleaning	Machine operator	Equipment usage/ cleaning logbook	Production manager
Visual inspection	Cleaning validation officer	Analytical logbook	Manager QA
Rinse sample	Machine operator/cleaning validation officer	Sampling sheet	Manager QA
pH/detergent	Cleaning validation officer/QC analyst	Analytical logbook	Validation/QC officer
Conductivity	Cleaning validation officer/QC analyst	Analytical logbook	Validation/QC officer
TOC	Cleaning validation officer/QC analyst	Analytical logbook	Validation/QC officer
MAC	Cleaning validation officer/QC analyst	Analytical logbook	QC analyst
Bio-burden	Cleaning validation officer/microbiologist	Analytical logbook	QC, manager microbiology-section

TOC, total organic carbon; MAC, maximum allowable carryover.

Performed by: _____ Date: _____

Checked by: _____ Date: _____

Your Company's Logo **Your Company's Name**

Attachment III

Training Record Verification

The following staff were found trained on cleaning of equipment.

Using SOP No. ABC-004; Revision No.; Issued on; Date

Name: _____ ID No.: _____ Sign.: _____ Date: _____

Name: _____ ID No.: _____ Sign.: _____ Date: _____

Performed by: _____ Date: _____

Checked by: _____ Date: _____

Your Company's Logo **Your Company's Name**

Attachment IV

Rinse Analysis Results

Sampling ID	Blank DIW			Rinse Sample					
	PH	**Conduc-tivity**	**TOC**	**Total Carryover HPLC Result**	**pH (Limit 5–7)**	**Conductivity NMT 5.0 µs/cm at 25°C**	**TOC NMT 500 ppb**	**Detergent Determination**	**Bio-Burden**
RN1									
RH1									
RT1									
RND1, RHD1 and RTD1									
HPLC chromatogram printouts should be attached to the analytical logbook.									

Performed by: _____ Date: _____

Checked by: _____ Date: _____

Your Company's Logo **Your Company's Name**

Attachment V

Swab Analysis Results

Sampling Location/ID	Visual Inspection	Carryover HPLC Result per 25 cm^2	25 cm^2 × Surface Area (Total Carryover)
S1			
S2			
S3			

Performed by: _____ Date: _____

Checked by: _____ Date: _____

CLV-37

Cleaning Validation Product Grouping Matrix (Sterile)

Your Company's Logo

Your Company's Name

Product	Ingredients	Batch Size	Maximum Usage per Day	Toxicity Level LD_{50}	Solubility
Vitamin B injection	B_1	304.8 kg	201 mg	>1000 mg/kg oral rat	2
	B_6			5500 mg/kg oral mouse	2
	B_{12}			>8000 mg/kg oral mouse	4
Bacitracin injection	Bacitracin USP	306.5 kg	2500 units	360 mg/kg IV mice	2
Cimetidine injection	Cimetidine	200 L	800 mg	5000 mg/kg oral rat	5
Diclofenac injection	Diclofenac	323.9 kg	150 mg	150 mg oral rat	4
Cyanocobalamin injection	Cyanocobalamin	100.3 kg	1000 mcg	>8000 mg/kg oral mouse	4
Calcitriol 1 mcg/mL	Calcitriol	123 L		0.62 mg oral rat	
Amikacin 500 mg/2 mL injection	Amikacin sulfate	174.15 kg	15 mg/kg/day	>6000 mg/kg oral mouse	2
Metoclopramide injection	Metoclopramide	200.6 kg	10 mg	280 mg/kg oral mouse	1
Ranitidine 50 mg/2 mL injection	Ranitidine HCl	216.64 kg	150 mg	4190 mg/kg oral rat	1
Omeprazole 40 mg injection	Omeprazole	113.339 kg	40 mg	2210 mg/kg oral rat	2
Hyoscine-*N*-butyl bromide 20 mg/1 mL injection	Hyoscine-*N*-butyl bromide	113 L	80 mg	1040 mg/kg oral rat	2
Vancomycin 0.5 g injection	Vancomycin HCl	336.6 kg	2.0 g	>10.0 g oral rat	2

CLV-38

Cleaning Validation Product/Equipment Train Matrix (Sterile)

Your Company's Logo

Your Company's Name

Product	Equipments
Vitamin B injection	Preparation vessel, mobile vessel, filtration assembly, ampoules filling and sealing machine
Bacitracin injection	Preparation vessel, mobile vessel, prefiltration and final filtration assembly, vial filling and sealing machine, freeze dryer
Cimetidine injection	Preparation vessel, mobile vessel, filtration assembly, ampoules filling and sealing machine
Diclofenac injection	Preparation vessel, mobile vessel, filtration assembly, ampoules filling and sealing machine
Cyanocobalamin injection	Preparation vessel, mobile vessel, filtration assembly, ampoules filling and sealing machine
Calcitriol 1 mcg/mL	Glass-lined preparation reactor 160 L, glass-lined mobile receiver 160 L, Sartorious pressure vessel 20 L, prefiltration 0.2 µ, filtration assembly B&S, ampoules filling and sealing machine
Amikacin 500 mg/2 mL injection	Preparation vessel, mobile vessel, filtration assembly, ampoules filling and sealing machine
Metoclopramide injection	Preparation vessel, mobile vessel, filtration assembly, ampoules filling and sealing machine
Ranitidine 50 mg/2 mL injection	Preparation vessel, mobile vessel, filtration assembly, ampoules filling and sealing machine
Omeprazole 40 mg injection	Preparation vessel, mobile vessel, filtration assembly, vial filling and sealing machine, freeze dryer
Hyoscine-*N*-butyl bromide 20 mg/1 mL injection	Preparation vessel, mobile vessel, filtration assembly, ampoules filling and sealing machine
Vancomycin 0.5 g injection	Preparation vessel, mobile vessel, prefiltration and final filtration assembly, vial filling and sealing machine, freeze dryer

CLV-39

Validation Protocols Biological and Sterile Products

CLV-39.1

Cleaning Validation Protocol for Freeze Dryer

Your Company's Logo

Your Company's Name

ABC Pharmaceutical Company	**CLEANING VALIDATION PROTOCOL** **Equipment Name**	
	Issued on **Date**	**Protocol Number** **CLVS-000**
	Location **Injectable Area** **Room No. 000**	

Equipment ..... **Equipment Name**

Model ..... **Model/Number**

Manufacturer ..... **Name and country**

Written by	**Signature & Date**
Validation Officer	_____
Reviewed by	**Signature & Date**
QA Manager	_____
	Signature & Date
QC Manager	_____
	Signature & Date
Production Manager	_____
Approved by	**Signature & Date**
Production Director	_____
Authorized by	**Signature & Date**
QA Director	_____

Your Company's Logo **Your Company's Name**

39.1.1 Objective

The objective is to demonstrate that the cleaning procedure will successfully and consistently reduce the level of residues to a predetermined level of acceptability, for the freeze dryer.

39.1.2 Scope

This protocol will cover cleaning of the freeze dryer for the following products. For each product, three lots will be tested. The cleaning validation approach is based on MAC limit of the active pharmaceutical ingredient, which is calculated on the basis of the worst-case scenario considering maximum daily dose of the batch manufactured:

- Bacitracin, USP
- Vancomycin HCl, USP

Following successful visual inspection and documentation of the cleaning of the equipment surfaces, the following programs are used:

- The equipment cleaning holding time is followed as per SOP No. ABC-001.
- The internal surfaces are subjected to clean in place (CIP) as per the procedure.

39.1.2.1 Cleaning Validation Program

At the end of vancomycin HCl injection manufacturing, the cleaning is performed as per the applicable SOP. The validation samples are collected at the end of cleaning and tested as per Tables 39.1.1 and 39.1.2. The approval to manufacture is granted by QA for the next product. The same approach is followed for bacitracin.

Product to be Manufactured	B. No.	Cleaning Time/Date	Sampling Time/Date	Testing Date	Desposition Accepted/Rejected
Vancomycin HCl					
Vancomycin HCl					
Vancomycin HCl					
Bacitracin					
Bacitracin					
Bacitracin					

Your Company's Logo **Your Company's Name**

TABLE 39.1.1

Surface Swabs Sampling Description

Description	Sample Location	Sample ID	Reference
Freeze dryer	Shelf no. 1 (top)	S1	Attachment III-Figure 39.1.1
	Shelf no. 2 (top)	S2	
	Shelf no. 3 (top)	S3	
	Shelf no. 4 (top)	S4	
	Shelf no. 5 (top)	S5	
	Shelf no. 6 (top)	S6	
	Shelf no. 7 (top)	S7	
	Shelf no. 8 (top)	S8	
	Shelf no. 9 (top)	S9	
	Shelf no. 10 (top)	S10	
	Shelf no. 11 (top)	S11	
	Shelf no. 12 (top)	S12	
	Shelf no. 1 (bottom)	S13	
	Shelf no. 2 (bottom)	S14	
	Shelf no. 3 (bottom)	S15	
	Shelf no. 4 (bottom)	S16	
	Shelf no. 5 (bottom)	S17	
	Shelf no. 6 (bottom)	S18	
	Shelf no. 7 (bottom)	S19	
	Shelf no. 8 (bottom)	S20	
	Shelf no. 9 (bottom)	S21	
	Shelf no. 10 (bottom)	S22	
	Shelf no. 11 (bottom)	S23	
	Shelf no. 12 (bottom)	S24	
	Wall (left)	S25	
	Wall (right)	S26	

TABLE 39.1.2

Rinse Sampling Description

Description	Sample Location	Sample ID
Freeze dryer	Drain sample point	R1-pH
		R1-conductivity
		R1-TOC
		R1-MAC
		R1-BB
		R1-endotoxin

Your Company's Logo

Your Company's Name

39.1.3 Responsibility

The following personnel are responsible for the execution of this protocol:

Cleaning validation officer/production officer/QA inspector/machine operator; for details, please refer to Attachment No. II.

39.1.4 Description of the Cleaning Process

The freeze dryer is cleaned as per SOP No. ABC-001.

39.1.5 Description of the Sampling Process

39.1.5.1 Sampling Technique

The following sampling techniques are used to take the sample for the freeze dryer:

a. Surface swabs (sterile swabs wetted with WFI)
b. Rinse sample (in a clean bottle)

39.1.5.2 Surface Swabs

39.1.5.2.1 Procedure for Sampling

Swab samples are prepared as per SOP No. ABC-002.

The cleaning validation officer is responsible for taking the swab sample.

Samples of the internal surfaces are taken by moistening the swab (ready-made sterile cotton swab) with a suitable solvent (water for injection).

Sample a 25-cm^2 area and place the swab in a test tube containing 10 mL of solvent (water for injection).

Open the chamber and take the sample from each shelf from the top side and the bottom side and from the walls in a sterile swab containing 10 mL WFI, as per Table 39.1.1.

39.1.5.3 Rinse Sampling

The rinse sample is taken from the bottom outlet of the freeze dryer.

The cleaning validation officer is responsible for collecting the sample for water rinses.

Your Company's Logo **Your Company's Name**

For the bio-burden test the sample is collected in a sterile bottle, and for the endotoxin test the sample is collected in de-pyrogenated bottles.

39.1.5.4 Sampling Precautions

Before taking the sample, wear the following:

a. Heat-resistant gloves
b. Safety goggles

39.1.6 Test Functions

a. *Visual inspection:* The pre- and postvisual inspection of the freeze dryer is performed as per Attachment No. VIII. The cleaning validation officer visualizes the equipment's outer and inner surfaces (difficult and not difficult to clean) to verify that the surfaces are free from any kind of visibly detectable residues.
b. *pH determination:* pH determination of the swab/rinse is performed as per the standard test method (STM PL-0021).
c. *Conductivity:* The test for conductivity of the rinse is performed as per SOP No. QCE-034.
d. *Maximum allowable carryover:* The test for MAC of the final swab is performed as per the following validated method for cleaning validation.
   - Vancomycin HCl
     Technique HPLC
     STM No ABC-0001
   - Bacitracin for injection, USP
     Technique HPLC
     STM No ABC-0002

   Note: By pooling the 10 mL swab extraction as required for specific analysis, anaysis of swab samples will be performed.
e. *Bio-burden test:* The test for bio-burden is performed as per STM No. ABC-0003 and SOP ABC-003 by the QC Microbiology section.
f. *Endotoxin test:* This test is performed as per the standard test method ABC-0004 by the QC Microbiology section.
g. *Swab sampling recovery challenge test:* The test to be performed is known as the concentration recovery test.

Your Company's Logo

Your Company's Name

39.1.7 Verification of Documents

a. Verify the freeze dryer cleaning procedure
b. Verify the CIP cycle printout
c. Verify the freeze dryer cleaning logbook record
d. Verify the staff training record (refer to Attachment No. IV)

39.1.8 Documentation

a. Printout of the CIP cycle
b. All analysis results are recorded in the analysis logbook; printouts and chromatograms are also attached with the logbook for reference
c. All analysis and data are verified by the second analyst
d. A cleaning validation officer checks all the training records
e. The final report for cleaning validation is prepared by the cleaning validation officer and subsequently reviewed and approved as per the procedure

39.1.9 Acceptance Criteria

a. *Visual Inspection:* The visible internal equipment surfaces and all critical and difficult-to-clean parts are optically free from residues.
b. *pH determination:* The pH value of the final rinse should be comparable to the blank WFI sample kept under the same condition (WFI pH limit 5–7).
c. *Conductivity:* The conductivity of the final rinse should be comparable to the blank WFI sample kept under the same conditions (WFI conductivity limit is 1.3 µs/cm at 25°C).
d. *Total organic carbon (TOC):* The TOC of the final rinse should be comparable to the blank WFI sample kept under the same conditions (WFI TOC limit is NMT 500 ppb).
e. *Maximum allowable carryover:* The active ingredient in the final rinse and swabs is either not detected or equal to or less than the MAC (calculated theoretically for each product) based on "worst-case" concept. The MAC is calculated for each product *t*. For each product, the MAC is calculated as follows:

$$\text{MAC} = \frac{\text{TD} \times \text{BS} \times \text{SF}}{\text{LDD}},$$

Your Company's Logo **Your Company's Name**

where MAC is the maximum allowable carryover, TD is a single therapeutic dose, BS is the batch size of the next product to be manufactured in the same equipment, SF is the safety factor, and LDD is the largest daily dose of the next product to be manufactured in the same equipment.

The calculated value is the maximum amount of active ingredient of a product that is allowed to be carried over to the next batch.

f. *Bio-burden:* The bio-burden should not be more than 10 cfu/100 mL for the rinses and not be more than 3 cfu/25 cm^2 for the swabs.

g. *Endotoxin*: The endotoxin should not be more than 0.25 EU/mL.

h. *Swab sampling recovery challenge test*: The swab recovery challenge test should be 95–105% of the known concentration of the standard spiked in a specific surface area.

39.1.10 List of Attachments

Attachment I	Description of product and equipment
Attachment II	Sampling technique
Attachment III	Equipment description and sampling locations
Attachment IV	Training record verification
Attachment V	Swabs analysis results
Attachment VI	Swab sampling recovery challenge test results

Your Company's Logo **Your Company's Name**

Attachment I

Description of Product and Equipment

Equipment Name: _____

Serial No.: _____

Capacity: _____

Calibrated on: _____

Location: _____

Room No.: _____

Previous Product: _____

Batch No. of the Previous Product: _____

Manufacturing Date: _____

Active Ingredient: _____

Therapeutic Group: _____

Cleaning Date: _____

Cleaning SOP No.: _____ Revision No.: _____

Sampling Technique: SOP No. ABC-003

Cleaning Sample Analysis Date: _____ Assay Result: _____

Test Method Reference: _____ Ref. Analytical Logbook: _____

Limit of Detection: _____

Next Product to Be Manufactured in the Same Equipment: _____

Safety Factor: _____

Your Company's Logo **Your Company's Name**

Attachment II

Sampling Technique

Product Name: _____

Batch No.: _____

Process Involved: _____

Sampling Location/ID	Sampling Criteria	Type of Sample	Sample Quantity	
	D	N	S	cm^2
R1		✓	Rinse	
S1		✓	✓	
S2		✓	✓	
S3		✓	✓	
S4		✓	✓	
S5		✓	✓	
S6		✓	✓	
S7		✓	✓	
S8		✓	✓	
S9		✓	✓	
S10		✓	✓	
S11		✓	✓	
S12		✓	✓	
S13		✓	✓	
S14		✓	✓	
S15		✓	✓	
S16		✓	✓	
S17		✓	✓	
S18		✓	✓	
S19		✓	✓	
S20		✓	✓	
S21		✓	✓	
S22		✓	✓	
S23		✓	✓	
S24		✓	✓	
S25		✓	✓	
S26		✓	✓	
S: Swab, D: Difficult to clean, N: Normal.				

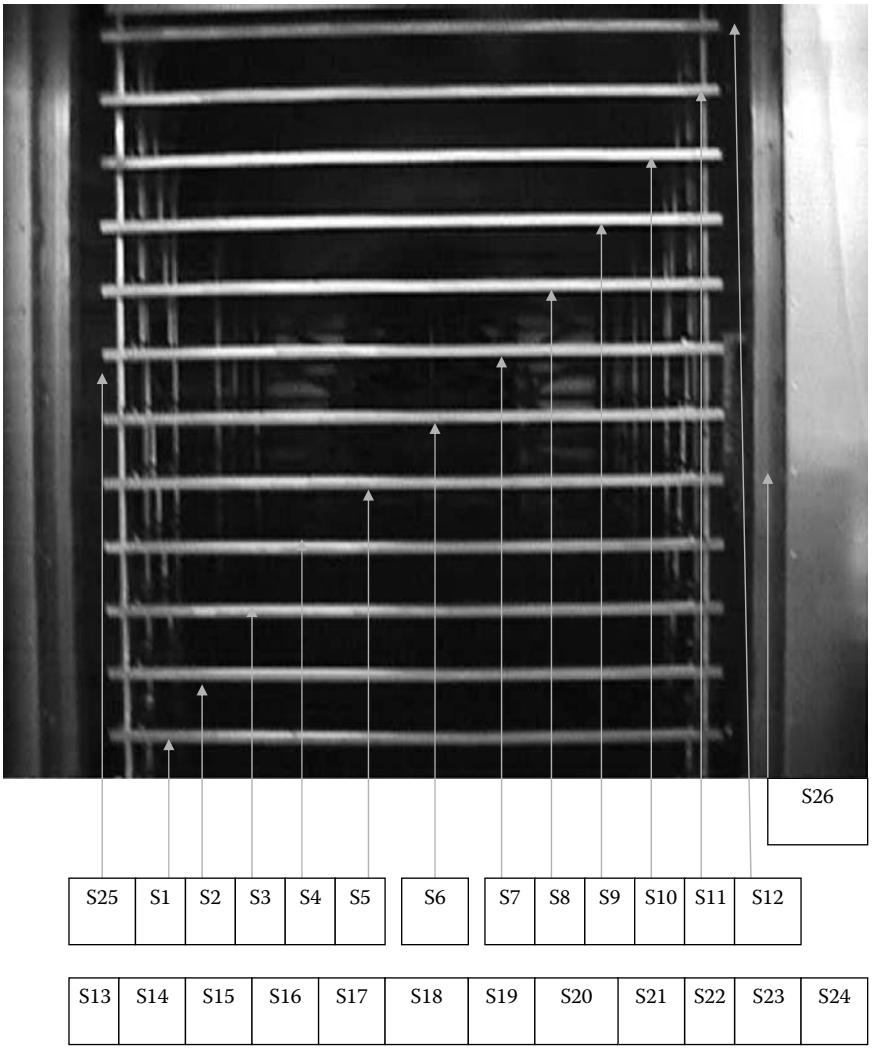
Product Name: _____ Date: _____

Checked Name: _____ Date: _____

Your Company's Logo **Your Company's Name**

Attachment III

Equipment Description and Sampling Locations



S1 to S12 (Bottom side of the trays) S13 to S24 (Top side of the trays)
S25 (left side wall) S26 (right side of the wall)

FIGURE 39.1.1
Top and bottom surface of the trays.

Your Company's Logo **Your Company's Name**

Attachment IV

Training Record Verification

The following staff were found trained on cleaning of the equipment.

Using SOP No. ABC-004; Revision No; Issued on; Date

Name: _____ ID No.: _____ Sign.: _____ Date: _____

Name: _____ ID No.: _____ Sign.: _____ Date: _____

Verified by: _____ Date: _____

Your Company's Logo

Your Company's Name

Attachment V

Swab Analysis Results

Sampling Location/ID	Visual Inspection		Carryover HPLC Result per 25 cm^2	Surface Area	Total Carryover
	Pre	Post			
S1					
S2					
S3					
S4					
S5					
S6					
S7					
S8					
S9					
S10					
S11					
S12					
S13					
S14					
S15					
S16					
S17					
S18					
S19					
S20					
S21					
S22					
S23					
S24					
S25					
S26					
Pre: before starting the manufacturing of tested batch, post: after the cleaning of tested batch.					

Your Company's Logo **Your Company's Name**

Rinse Analysis Results

Sampling Location	Blank WFI			Sample					
	PH	Conductivity	TOC	Total Carryover HPLC Result	pH (Limit 5–7)	TOC NMT 500 ppb	Conductivity NMT 1.3 µs/cm at 25°C	Bio-Burden Test NMT 10 cfu/100 mL	Endotoxin Test NMT 0.25 EU/mL
R1									

Product Name: _____ Date: _____

Checked Name: _____ Date: _____

Your Company's Logo **Your Company's Name**

Attachment VI

Swab Sampling Recovery Challenge Test

Name of Active Material	Concentration of Standard Solution	Type of Swab	Total Area of Swab	% Recovery of Active Ingredient	% Recovery as per Limit NLT (70%)	
					Y	N

Product Name: _____ Date: _____

Checked Name: _____ Date: _____

CLV-39.2

Cleaning Validation Protocol for Glass-Lined Mobile Tank

Your Company's Logo

Your Company's Name

ABC Pharmaceutical Company	**CLEANING VALIDATION PROTOCOL** **Equipment Name**	
	Issued on **Date**	**Protocol Number** **CLVS-000**
	Location **Injectable Area** **Room No. 000**	

Equipment . . . . . **Equipment name**

Model . . . . . **Model/Number**

Manufacturer . . . . . **Name and Country**

Written by	**Signature & Date**
Validation Officer	_____
Reviewed by	**Signature & Date**
QA Manager	_____
	Signature & Date
QC Manager	_____
	Signature & Date
Production Manager	_____
Approved by	**Signature & Date**
Production Director	_____
Authorized by	**Signature & Date**
QA Director	_____

Your Company's Logo **Your Company's Name**

39.2.1 Objective

The objective of this protocol is to demonstrate that the cleaning procedure will successfully and consistently reduce the level of residue to a predetermined level of acceptability, for the glass-lined mobile tank.

39.2.2 Scope

This protocol will cover cleaning of the glass-lined mobile tank for calcitriol 1 mcg/mL injection as the worst-case product. The cleaning validation approach is based on verification of cleaning after the manufacture of calcitriol 1 mcg/mL injection

39.2.2.1 Cleaning Validation Program

At the end of calcitriol 1 mcg/mL manufacturing, the cleaning is performed as as per the applicable SOP No. ABC-001. The validation samples are collected at the end of cleaning and then tested.

Product to be Manufactured	B. No.	Cleaning Date	Sampling Date	Testing Date	Desposition Accepted/Rejected
Calcitriol 1 mcg/mL injection	First				
Calcitriol 1 mcg/mL injection	Second				
Calcitriol 1 mcg/mL injection	Third				

39.2.3 Responsibilities

The following personnel are responsible for the execution of this protocol:

> Cleaning validation officer/production officer/QA inspector/machine operator/QC analyst

39.2.4 Description of the Cleaning Process

The glass-lined mobile tank is cleaned by the CIP procedure as per SOP No. ABC-002.

1. Switch on the main switch on the control panel.
2. Make sure of the following:
   a. The tank lid is closed and secured by swinging safety bolts.

b. The tank outlet valve is open.
c. All other valves and sockets are closed.
d. Connect the nitrogen use point to the nitrogen inlet valve.

3. Connect the tank outlet valve with the drain use point and open the drain valve.
4. Connect the DIW use point to the CIP inlet valve of the tank.
5. Open the DIW valve completely.
6. Open the spray ball inlet valve of the tank for five pulses, each pulse with 20 kg DIW (as seen on the load cells display of the preparation tank) and between each pulse and another wait until the DIW drains completely from the tank (pressurize the tank with nitrogen up to 1 bar, if necessary, to drain the DIW).
7. Close the tank outlet valve.
8. On the WFI control panel, push the "HOT" button followed by "START."
9. Open the tank outlet valve.
10. After flushing with 20 kg hot WFI, push the "STOP" button on the WFI panel.
11. Cover the mixer with 50 L hot WFI and operate for 2 min (at 150 rpm).
12. Stop the mixer; apply a pressure of 1 bar to allow WFI to drain out.
13. After WFI drains completely, close the tank outlet valve.
14. Apply nitrogen through the tank vent valve.
15. Open the tank outlet valve and allow the residual water to dry with nitrogen flow for 30 min.

39.2.5 Identification of Critical Parameters

The critical parameters are monitored by the online monitoring system as stated in Table 39.2.1.

Critical parameters were set as per the manufacturing guidelines of CIP in SOP No. ABC-002 and it is important to follow the set temperature and volume of DIW and WFI to perform cleaning of the glass-lined mobile tank.

39.2.6 Description of the Sampling Process

39.2.6.1 Sampling Technique

The following sampling techniques are used to take the sample for the mobile tank:

a. Surface swabs (sterile cotton swabs wetted with WFI)
b. Water rinses (in clean bottle)

Your Company's Logo

Your Company's Name

TABLE 39.2.1

Critical Parameters

Parameters	Specification	Actual Reading
Temperature of DIW water	25°C	
Volume of DIW in tank, step 1	20 kg (L)	
Volume of DIW in tank, step 2	20 kg (L)	
Volume of DIW in tank, step 3	20 kg (L)	
Volume of DIW in tank, step 4	20 kg (L)	
Volume of DIW in tank, step 5	20 kg (L)	
Volume of DIW in tank, step 6	50 kg (L)	
Temperature of WFI	NLT80°C	
Volume of WFI in tank, step 1	20 kg (L)	
Volume of WFI in tank, step 2	20 kg (L)	
Volume of WFI in tank, step 3	50 kg (L)	

39.2.6.2 Surface Swabs

39.2.6.2.1 Procedure for Sampling

Sampling is performed as per SOP No. ABC-003.

The cleaning validation officer is responsible for taking the swab samples.

Samples of the internal surfaces should be taken by moistening the swab (ready-made sterile cotton swab) with a suitable solvent (water for injection).

Sample a 25-cm^2 area and place the swab in a test tube containing 10 mL of solvent (water for injection).

Swab samples from each part of the mobile receiver are collected as per Table 39.2.2.

39.2.6.3 Water Rinses

39.2.6.3.1 Procedure for the Sample

Water rinse is collected as per SOP No. ABC-004.

The cleaning validation officer is responsible for collecting the sample for water rinses.

TABLE 39.2.2

Surface Swabs Sampling Description

Description	Sample Location	Sample ID	Reference
Mobile tank	Outer surface wall	S1	Attachment III-Figure 39.2.2
	Outer surface lid	S2	
	Outer surface top left	S3	Attachment III-Figures 39.2.2 and 39.2.3
	Outer surface tubing	S4	
	Outer surface top right	S5	

Your Company's Logo **Your Company's Name**

TABLE 39.2.3

Rinse Sampling Description

Description	Sample Location	Sample ID	Reference
Mobile tank	Mobile tank outlet valve	R1-pH R1-conductivity R1-TOC R1-MAC R2-BB R3-endotoxin	Attachment III-Figure 39.2.2

For the bio-burden test, the sample is collected in a sterile bottle, and for the endotoxin test the sample is collected in de-pyrogenated bottles. For sampling descriptions see Table 39.2.3.

39.2.6.4 Sampling Precautions

Before taking the sample, wear the following:

i. Heat-resistant gloves
ii. Safety goggles

Open the tank outlet valve slowly and collect the sample in labeled bottles as stated in Table 39.2.4.

39.2.7 Test Functions

a. *Visual inspection*: The postvisual inspection of the glass-lined mobile tank is performed as per Attachment V. The cleaning validation officer will visualize the

TABLE 39.2.4

Sampling and Testing Plan

S. No.	Test	Identification Labeling	Sample Volume (mL)	Sampling Bottle	Testing Specifications	Testing Method/ Procedure No.
1	pH	R1-pH	100	Clean bottle	5–7 pH unit	STM-ABC-0001
2	Conductivity	R1-conductivity	100	Clean bottle	NMT 5.0 µs/cm	
3	TOC	R1-TOC	50	Clean bottle	NMT 500 ppb	SOP-ABC-005
4	Calcitriol	R1-MAC	50	Clean bottle	NMT MAC	Validated HPLC method
5	Bio-burden	R2-microbiology	100	Sterilized bottle	NMT 10 cfu/100 mL	STM-ABC-0003
6	Endotoxin	R3	100	De-pyrogenated bottle	Endotoxin test NMT 0.25 EU/mL	STM-ABC-0004

Your Company's Logo **Your Company's Name**

equipment's outer and inner surfaces (difficult to clean) to verify that the surfaces are free from any kind of visibly detectable residue.

b. *pH determination*: pH determination of the final rinse is performed as per the standard test method (STM No. ABC-0005).

c. *Conductivity*: The test for conductivity of the final rinse is performed as per SOP ABC-0001.

d. *Total organic carbon*: The test for TOC of the final rinse is performed as per SOP ABC-005.

e. *Calcitriol test*: The test for calcitriol of the final rinse/swab is performed as per the following validated method for cleaning validation.

Note: By pooling the 10 mL swab extraction as required for specific analysis, analysis of swab samples is performed.

f. *Bio-burden test*: The test for bio-burden is performed as per STM ABC-0003 by the QC Microbiology section.

g. *Endotoxin test*: This test is performed as per the standard test method ABC-0004 by the QC Microbiology section.

Note: Test functions d, f, and g are not applicable to swab samples. They are applied only to rinse samples.

39.2.8 Verification of Documents

a. Verify the glass-lined mobile tank cleaning procedure

b. Verify the CIP cycle printout

c. Verify the glass-lined mobile tank cleaning logbook records

d. Verify the staff training record

39.2.9 Documentation

a. All analysis results are recorded in the analysis logbook.

b. Printouts and chromatograms are attached to the validation report and a copy of that is also attached to the analytical logbook.

c. All training records are checked by the cleaning validation officer.

d. The final report for cleaning verification should be prepared by the cleaning validation officer, and subsequently reviewed and approved as per the procedure.

Your Company's Logo **Your Company's Name**

39.2.10 Acceptance Criteria

a. *Visual inspection*: The visible internal equipment surfaces and all critical and difficult-to-clean parts are optically free from residue and the color of the final rinse water is comparable to WFI.

b. *pH determination*: The pH value of the final rinse should be comparable to the blank WFI sample kept under the same condition (WFI pH limit 5–7).

c. *Conductivity*: The conductivity of the final rinse should be comparable to the blank WFI sample kept under the same conditions (WFI conductivity limit is 1.3 µs/cm at 25°C).

d. *Total organic carbon*: The TOC of the final rinse should be comparable to the blank WFI sample kept under the same conditions (WFI TOC limit is NMT 500 ppb).

e. *Calcitriol contamination carryover*: The contamination and traces of the calcitriol in the final rinse and swabs are either not detected or equal to or less than the MAC.

f. *Bio-burden*: The bio-burden should not be more than 10 cfu/100 mL for the rinses and not more than 3 cfu/25 cm^2 for the swabs.

g. *Endotoxin:* The endotoxin should not be more than 0.25 EU/mL.

39.2.11 List of Attachments

Attachment I	Description of equipment and product
Attachment II	Sampling and testing plan
Attachment III	Equipment description and sampling locations
Attachment IV	Training record verification
Attachment V	Swab sampling and rinse analysis results

Your Company's Logo **Your Company's Name**

Attachment I

Description of Equipment and Product

Equipment Name: Glass-lined mobile tank

Serial No.: _____

Capacity: 150 L

Location: Solution preparation room

Room No.: _____

Previous Product: _____

Batch No. of the Product: _____

Manufacturing Date: _____

Active Ingredient: _____

Therapeutic Group: _____

Cleaning Date: _____

Cleaning SOP No. _____ Revision No. _____

Sampling Technique: ABC-003

Cleaning Sample Analysis Date/Time: _____ Assay Result: _____

Test Method Reference: _____ Reference Analytical Logbook: _____

Limit of Detection: _____

Safety Factor: _____

Your Company's Logo **Your Company's Name**

Attachment II

Sampling Technique

Test	Identification	Equipment Surface	Sample Area	Testing Specification	Test Method
Calcitriol	S1	Outer surfaces	25 cm^2	Not detected/less than the limit of detection	Validated HPLC method
	S2				
	S3				
	S4				
	S5				

Performed by: _____ Date: _____

Checked by: _____ Date: _____

Your Company's Logo **Your Company's Name**

Attachment III

Equipment Description and Sampling Locations

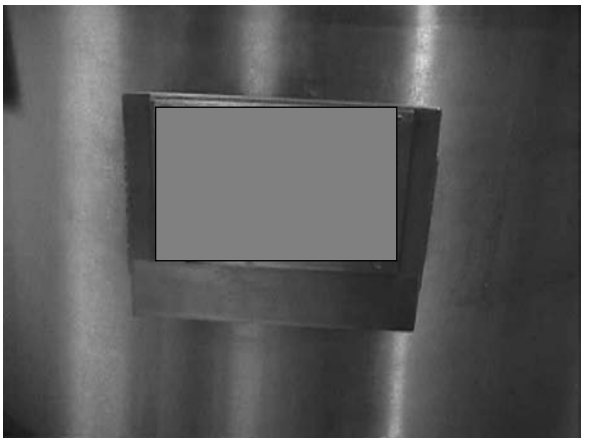


FIGURE 39.2.1
Mobile tank (front view).

FIGURE 39.2.2
Swab sampling points.

Your Company's Logo **Your Company's Name**

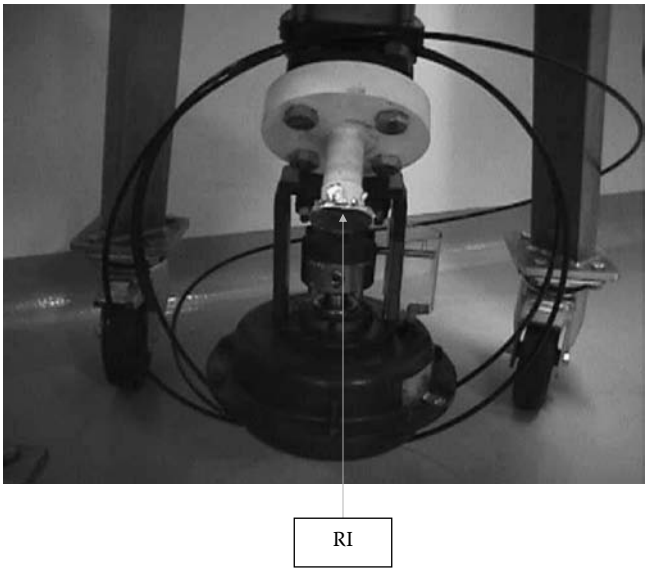


FIGURE 39.2.3
Rinse sampling points.

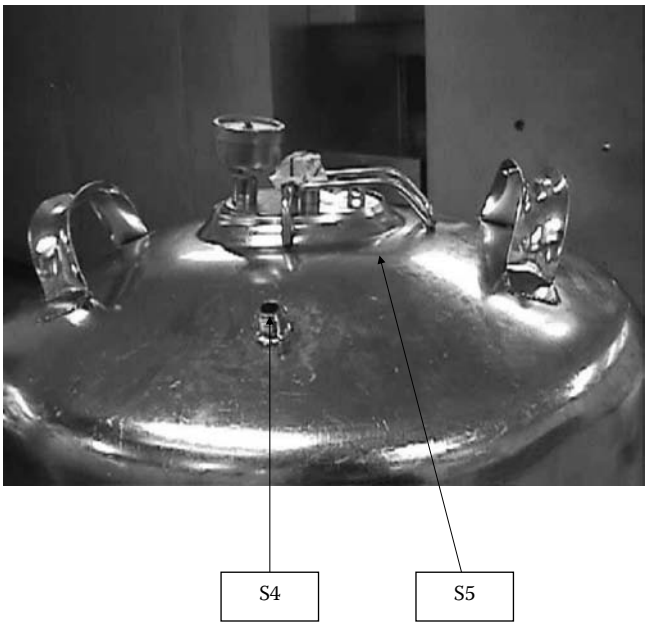


FIGURE 39.2.4
Mobile tank outer surface tubing and outer surface top.

Your Company's Logo **Your Company's Name**

Attachment IV

Training Record Verification

The following staff training record was checked and found trained:

Using SOP No. ABC-006; Revision No.; Issue date; Date

Name: _____ ID No.: _____ Sign.: _____ Date: _____

Name: _____ ID No.: _____ Sign.: _____ Date: _____

Verified by: _____ Date: _____

Your Company's Logo **Your Company's Name**

Attachment V

Swabs and Rinse Analysis Results

Swab Analysis Results

Sampling Location/ID	Visual Inspection	Carryover HPLC Result per 25 cm^2	Total Carryover
S1			
S2			
S3			
S4			
S5			

Rinse Analysis Results

Sampling Location	Blank WFI			Sample					
	pH	Conductivity	TOC	Total Carryover HPLC Result	pH (Limit 5–7)	TOCNMT 500 ppb	Conductivity NMT 1.3 µs/cm at 25°C	Bio-Burden Test NMT 10 cfu/100 mL	Endotoxin Test NMT 0.25 EU/mL
R1								–	–
R2				–	–	–	–		–
R3				–	–	–	–	–	

Note: The HPLC chromatogram printout should be attached to the analytical logbook.

Performed by: _____ Date: _____

Checked by: _____ Date: _____

CLV-39.3

Protocol for Preparation and Holding Vessel for Egg Protein

Your Company's Logo

Your Company's Name

ABC Pharmaceutical Company	**CLEANING VALIDATION PROTOCOL** **Equipment Name**	
	Issued on: **Date**	**Protocol Number** **CLVS-000**
	Location **Sterile Preparation Area**	

Equipment Name..... Preparation and Holding Vessels (60 L)

Model..... Model and make

Manufacturer ..... Company and country

39.3.1 Objective

The objective of this protocol is to demonstrate and document that the cleaning procedure will successfully and consistently reduce the level of residues to a predetermined level of acceptability for the preparation and holding vessels ABC-1 and ABC-2.

39.3.2 Scope

This protocol will cover the cleaning process of the preparation and holding vessels for egg protein 4000 units/vial and egg protein 2000 units/vial.

Your Company's Logo **Your Company's Name**

39.3.3 Cleaning Validation Approach

Erythropoietin is manufactured in two strengths of recombinant human erythropoietin, which are 4000 and 2000 units/vial. Since both the strengths are manufactured in the same preparation and holding vessels, only the higher strength, erythropoietin 4000 units/vial, is considered as the worst case for the cleaning validation study under this protocol.

39.3.4 Responsibilities

The following personnel are responsible for the execution of this protocol:

The cleaning validation officer is responsible for the cleaning validation protocol write up, execution, and report writing.

The production officer and the machine operator are responsible for cleaning the equipment as per the approved procedure.

The QA inspector is responsible for system compliance.

The QC analyst is responsible for performing analysis of the cleaning samples as per the approved protocol and test method.

39.3.5 Description of the Cleaning Process

The preparation tank should be cleaned manually as per SOP No. ABC-001

39.3.6 Description of the Sampling Process

39.3.6.1 Sampling Technique

The sampling and testing are carried out as per the attached sampling and testing plan and the figure of the corresponding equipment (Tables 39.3.1 through 39.3.3 and Figures 39.3.1 and 39.3.2).

Your Company's Logo

Your Company's Name

39.3.6.2 Procedure for Sample

The water rinse is collected as per SOP No. ABC-002.

The cleaning validation officer is responsible for collecting the sample for water rinses in clean bottles.

For the bio-burden test the sample is collected in a sterile bottle, and for the endotoxin test the sample is collected in de-pyrogenated bottles.

39.3.6.3 Surface Swabs

Samples of the internal surfaces should be taken by moistening the swab (ready-made sterile cotton swab) with a suitable solvent (WFI). Sample a 25-cm^2 area and place the swab in a test tube containing 10 mL of solvent (WFI) (Table 39.3.1).

After the cleaning of the vessel, the final rinse is collected from the sampling point in a labeled bottle as stated in the sampling and testing plan. The swab sample is taken as per the figures.

39.3.6.4 Sampling Precautions

Before taking the sample, wear the following:

i. Heat-resistant gloves
ii. Safety goggles

TABLE 39.3.1

Rinse Sampling Description

Description	Sample ID	Reference
Preparation vessel	RP1[a]-pH	As per the sampling and testing plan
	RP1-conductivity	
	RP1-TOC	
	RP1-MAC	
	RP2-BB	
	RP3-endotoxin	
Holding vessel	RH1-pH[b]	As per the sampling and testing plan
	RH1-conductivity	
	RH1-TOC	
	RH1-MAC	
	RH2-BB	
	RH3-endotoxin	

[a] Rinse preparation vessel.
[b] Rinse holding vessel.

Your Company's Logo

Your Company's Name

TABLE 39.3.2

Swab Sampling Description

Test	Identification Labeling	Equipment Surface	Sample Area	Testing Specifications	Testing Method/ Procedure No.
Epotin	PS1[a]	Outer surface 1	25 cm^2	Not detected/less than the limit of detection	Validated HPLC method
	PS2	Outer surface 2			
	PS3	Inner surface 1			
	PS4	Inner surface 2			
Epotin	HS1[b]	Outer surface 1	25 cm^2	Not detected/less than the limit of detection	Validated HPLC method
	HS2	Outer surface 2			
	HS3	Inner surface 1			
	HS4	Inner surface 2			

[a] Preparation vessel swab
[b] Holding vessel swab

39.3.6.5 Sampling and Testing Plan (Table 39.3.3)

TABLE 39.3.3a

Preparation Vessel (Rinse Sample)

S. No.	Test	Identification Labeling	Sample Volume	Sampling Bottle	Testing Specifications	Testing Method/ Procedure No.
1	pH	RP-1	100 mL	Clean bottle	5–7 pH unit	ABC-001
2	Conductivity				NMT 5.0 µs/cm	ABC-002
3	TOC				NMT 500 ppb	SOPABC-003
4	Epotin				Not detected/less than the limit of detection	Validated HPLC method
5	Bio-burden	RP-2	100 mL	Sterilized bottle	NMT 10 cfu/100 mL	STM-MC-001
6	Endotoxin	RP-3	100 mL	De-pyroginated bottle	0.25 EU/mL	*MC-002*

RP, rinse preparation vessel.

Performed by: _____ Date _____

Checked by: _____ Date _____

Your Company's Logo **Your Company's Name**

39.3.6.6 Preparation Vessel (Swab Sample)

Test	Identification Labeling	Equipment Surface	Sample Area	Testing Specifications	Testing Method/ Procedure No.
Epotin	PS1	Outer surface 1	25 cm^2	Not detected/less than the limit of detection	Validated HPLC method
	PS2	Outer surface 2			
	PS3	Inner surface 1			
	PS4	Inner surface 2			

Performed by: _____ Date _____

Checked by: _____ Date _____

39.3.6.7 Sampling and Testing Plan

TABLE 39.3.3b

Holding Vessel (Rinse Sample)

S. No.	Test	Identification Labeling	Sample Volume	Sampling Bottle	Testing Specifications	Testing Method/ Procedure No.
1	pH	RH-1	100 mL	Clean bottle	5–7 pH unit	ABC-001
2	Conductivity				NMT 5.0 µs/cm	ABC-002
3	TOC				NMT 500 ppb	SOP ABC-003
4	Epotin				Not detected/less than the limit of detection	Validated HPLC method
5	Bio-burden	RH-2	100 mL	Sterilized bottle	NMT 10 cfu/100 mL	STM-MC-001
6	Endotoxin	RH-3	100 mL	De-pyroginated bottle	0.25 EU/mL	MC-002

RH, rinse holding vessel.

Performed by: _____ Date _____

Checked by: _____ Date _____

Your Company's Logo **Your Company's Name**

39.3.6.8 Holding Vessel (Swab Sample)

Test	Identification Labeling	Equipment Surface	Sample Area	Testing Specifications	Testing Method/ Procedure No.
Epotin	HS5	Outer surface 1	25 cm^2	Not detected/less than the limit of detection	Validated HPLC method
	HS6	Outer surface 2			
	HS7	Inner surface 1			
	HS8	Inner surface 2			

Performed by: _____ Date _____

Checked by: _____ Date _____

39.3.7 Test Functions

39.3.7.1 Visual Inspection

The visual inspection of preparation and holding vessels should be performed. The cleaning validation officer visualizes the equipment's outer and inner surfaces (difficult and not difficult to clean) to verify that the surfaces are free from any kind of visibly detectable residue.

39.3.8 Verification of Document

a. Verify the preparation and holding vessel cleaning procedure.
b. Verify the preparation and holding vessel cleaning logbook records.
c. Verify the staff training record (refer to Attachment II).

39.3.9 Documentation

a. All analysis results are recorded in the analysis logbook.
b. Printouts and chromatograms are attached to the validation report and a copy of that is also attached to the analytical logbook.
c. The final report for cleaning validation should be prepared by the cleaning validation officer, and subsequently reviewed and approved as per the procedure.

Your Company's Logo **Your Company's Name**

39.3.10 Acceptance Criteria

a. *Visual inspection*: The visible internal equipment surfaces and all critical and difficult-to-clean parts are optically free from residue and the color of the final rinse water is comparable to WFI.

b. *pH determination*: The pH value of the final rinse should be comparable to the blank WFI sample kept under the same conditions (WFI pH limit 5–7).

c. *Conductivity*: The conductivity of the final rinse should be comparable to the blank WFI sample kept under the same conditions (WFI conductivity limit is 1.3 µs/cm at 25°C).

d. *Total organic carbon*: The TOC of the final rinse should be comparable to the blank WFI sample kept under the same conditions (WFI TOC limit is NMT 500 ppb).

e. *Active ingredient detection*: The active ingredient in the final rinse/swabs should be either not detected or less than the limit of detection of egg protein.

f. *Bio-burden*: The bio-burden should not be more than 10 cfu/100 mL for the rinses

g. *Endotoxin*: The endotoxin should not be more than 0.25 EU/mL.

39.3.11 List of Attachments

Attachment I	Description of equipment and product
Attachment II	Training record verification
Attachment III	Rinse/swab analysis results

Your Company's Logo **Your Company's Name**

Attachment I

Description of Equipment and Product

Equipment Name: _____

Serial No.: _____

Capacity: _____

Location: _____

Room No.: _____

Previous Product: _____

Batch No. of the Product: _____

Manufacturing Date: _____

Active Ingredient: _____

Therapeutic Group: _____

Cleaning Date: _____

Cleaning SOP No.: _____ Revision No.: _____

Sampling Technique: _____

Cleaning Sample Analysis Date/Time: _____

Test Method Reference: _____ Reference Analytical Logbook: _____

Limit of Detection: _____ Result: _____

Safety Factor: _____

Performed by: _____ Date _____

Checked by: _____ Date _____

Your Company's Logo **Your Company's Name**

Attachment II

Training Record Verification

The following staff training record was checked and found trained.

Using SOP No. ABC-004; Revision No.; Issued on; Date

Name: _____ ID.No.: _____ Sign.: _____ Date: _____

Verified by: _____ Date: _____

Your Company's Logo

Your Company's Name

Attachment III

Rinse/Swab Analysis Results

Rinse Analysis Results (Preparation Vessel)

Sampling Identification	Blank WFI			Sample					
	pH	Conductivity	TOC	Total Carryover HPLC Result	pH (Limit 5–7)	TOC NMT 500 ppb	Conductivity NMT 1.3 µs/cm at 25°C	Bio-Burden Test NMT 10 cfu/100 mL	Endotoxin Test NMT 0.25 EU/mL
RP-1								–	–
RP-2				–	–	–	–		–
RP-3				–	–	–	–	–	

Swab Analysis Results (Preparation Vessel)

Swab ID	Visual Inspection	Carryover HPLC Results per 25 cm²	Total Carryover
PS1			
PS2			
PS3			
PS4			

Rinse Analysis Results (Holding Vessel)

Sampling Identification	Blank WFI			Sample					
	pH	Conductivity	TOC	Total Carryover HPLC Result	pH (Limit 5–7)	TOC NMT 500 ppb	Conductivity NMT 1.3 µs/cm at 25°C	Bio-Burden Test NMT 10 cfu/100 mL	Endotoxin Test NMT 0.25 EU/mL
RH-1								–	–
RH-2				–	–	–	–		–
RH-3				–	–	–	–	–	

Your Company's Logo **Your Company's Name**

Swab Analysis Results (Holding Vessel)

Swab ID	Visual Inspection	Carryover HPLC Results per 25 cm^2	Total Carryover
HS5			
HS6			
HS7			
HS8			

*HPLC chromatogram printout should be attached to the analytical logbook.

Performed by: _____ Date: _____

Checked by: _____ Date: _____

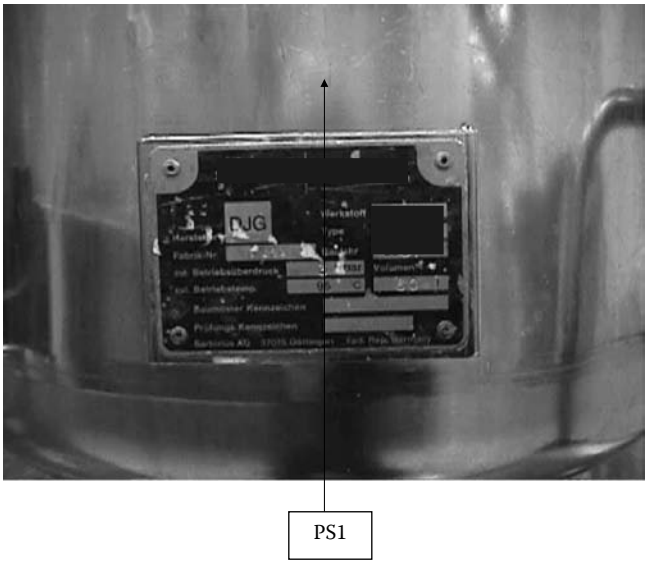


FIGURE 39.3.1
Front view of the holding vessel and swab sampling location.

Your Company's Logo **Your Company's Name**

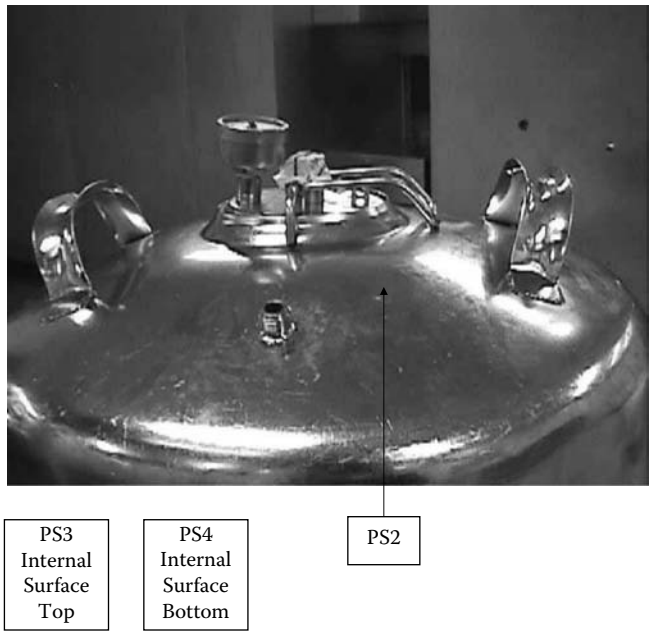


FIGURE 39.3.2
Top surface of the holding vessel.

CLV-39.4

Protocol for Filtration Assembly

Your Company's Logo

Your Company's Name

ABC Pharmaceutical Company	**CLEANING VALIDATION PROTOCOL** **Equipment Name**	
	Issued on **Date**	**Protocol Number** **CLVS-000**
	Location **Sterile Filling Area**	

Equipment Name..... Filtration Assembly

Model..... Model and Number

Manufacturer ..... Company and country

39.4.1 Objective

The objective of this protocol is to demonstrate that the cleaning procedure will successfully and consistently reduce the level of residues to a predetermined level of acceptability, for the filtration assembly and filling machine parts.

39.4.2 Scope

This protocol will cover the cleaning process of the filtration assembly and filling machine parts for the worst-case products selected from the injectable products matrix (Table 39.4.1). For each product three lots should be tested. The cleaning validation approach is based on the MAC limit of the active pharmaceutical ingredient, which is calculated on the basis of the worst-case scenario considering the maximum daily dose and the smallest batch size of the batch manufactured. Filter cartridges are single use only for each batch.

Your Company's Logo

Your Company's Name

TABLE 39.4.1

Injectable Products Matrix

Product	Ingredients	Batch Size	Maximum Usage per Day	Toxicity Level LD_{50}	Solubility
Vitamin B injection	B_1	304.8 kg	201 mg	>1000 mg/kg oral rat	2
	B_6			5500 mg/kg oral mouse	2
	B_{12}			>8000 mg/kg oral mouse	4
Bacitracin injection	Bacitracin USP	306.5 kg	2500 units	360 mg/kg IV mice	2
Cimetidine injection	Cimetidine	200 L	800 mg	5000 mg/kg oral rat	5
Diclofenac injection	Diclofenac	323.9 kg	150 mg	150 mg oral rat	4
Cyanocobalamin injection	Cyanocobalamin	100.3 kg	1000 mcg	>8000 mg/kg oral mouse	4
Calcitriol 1 mcg/mL	Calcitriol	123 L		0.62 mg oral rat	
Amikacin 500 mg/2 mL injection	Amikacin sulfate	174.15 kg	15 mg/kg/day	>6000 mg/kg oral mouse	2
Metoclopramide injection	Metoclopramide	200.6 kg	10 mg	280 mg/kg oral mouse	1
Ranitidine 50 mg/2 mL injection	Ranitidine HCl	216.64 kg	150 mg	4190 mg/kg oral rat	1
Omeprazole 40 mg injection	Omeprazole	113.339 kg	40 mg	2210 mg/kg oral rat	2
Hyoscine-*N*-butyl bromide 20 mg/1 mL injection	Hyoscine-*N*-butyl bromide	113 L	80 mg	1040 mg/kg oral rat	2
Vancomycin 0.5 g injection	Vancomycin HCl	336.6 kg	2.0 g	>10.0 g oral rat	2

Filtration assembly housing and connections include the following:

Prefiltration
Final filtration
Upstream silicon hose (product dedicated)
Downstream silicon hose (product dedicated)
Filling machine parts
Buffer tank
Pipe to manifold
Manifold

Your Company's Logo **Your Company's Name**

Prepump silicon hose (product dedicated)
Pumps
Postpump silicon hose (product dedicated)
Filling needles
Vibratory sorters for stopper
Stopper feed track
For the products of

- Bacitracin injection, USP
- Vancomycin HCl, USP

After successful visual inspection and documentation of the cleaning of the equipment surfaces, the following programs are used:

The equipment cleaning holding time is followed as per SOP No. ABC-001.
The internal surfaces are subjected to CIP as per the approved procedure.

39.4.3 Responsibility

The following personnel are responsible for the execution of this protocol:

Cleaning validation officer/production officer/QA inspector/machine operator

39.4.4 Description of the Cleaning Process

Filtration assembly and filling machine parts should be cleaned by using SOP No. ABC-002.

39.4.4.1 Sampling Technique

The following sampling technique is used for taking sample filtration assembly and filling machine parts.

a. Surface swabs (sterile cotton swabs wetted with WFI)
b. Water rinses (in clean bottle as listed below)

Your Company's Logo

Your Company's Name

TABLE 39.4.2

Surface Swabs Sampling Description

Description	Sample Location	Sample ID	Reference
Filling needles	Filling needle	S1	Attachment III-Figure 39.4.2
	Filling needle	S2	
	Filling needle	S3	
	Filling needle	S4	
Pumps	Pumps	S5	Attachment III-Figure 39.4.2
	Pumps	S6	
	Pumps	S7	
	Pumps	S8	
Minifold	Manifold	S9	Attachment III-Figure 39.4.2
	Manifold	S10	
	Manifold	*S11*	
	Manifold	S12	
Prepump silicon hose	Prepump silicon hose	S13	
	Prepump silicon hose	S14	
	Prepump silicon hose	S15	
	Prepump silicon hose	S16	
Postpump silicon hose	Postpump silicon hose	S17	
	Postpump silicon hose	S18	
	Postpump silicon hose	S19	
	Postpump silicon hose	S20	
Vibratory sorters	Vibratory sorters	S21	Attachment III-Figure 39.4.3
	Vibratory sorters	S22	
	Vibratory sorters	S23	
Stopper feed track	Stopper feed track	S24	
	Stopper feed track	S25	
	Stopper feed track	S26	

39.4.4.2 Procedure for Sampling

39.4.4.2.1 Surface Swabs

Sampling is performed as per SOP No. ABC-003; the cleaning validation officer is responsible for taking the swab sample. Samples of the internal surfaces are taken by moistening the swab (ready-made sterile cotton swab) with a suitable solvent (water for injection). Sample a 25-cm^2 area and place the swab in a test tube containing 10 mL of solvent (water for injection). Swab samples from each part of the filtration assembly and filling machine parts are collected as per Tables 39.4.2 and 39.4.3.

Your Company's Logo

Your Company's Name

TABLE 39.4.3

Rinse Sampling Description

Description	Sample Location	Sample ID	Reference
Filtration			Attachment III-Figure 39.4.1
	Prefiltration	R1	
Buffer tank	Final filtration	R2	
	Outlet valve	R3	

39.4.4.2.2 Water Rinses

The water rinse is collected as per SOP No. ABC-004.

The water rinse sample is collected in a labeled clean bottle as per Table 39.4.3.

The cleaning validation officer is responsible for collecting the sample for water rinses.

For the bio-burden test the sample is collected in a sterile bottle, and for the endotoxin test the sample is collected in de-pyrogenated bottles.

39.4.4.3 Sampling Precautions

Before taking the sample, wear the following:

i. Heat-resistant gloves
ii. Safety goggles

Samples of water rinse should be collected from the outlet valve of the filtration assembly (prefiltration and sterile filtration) after the completion of cleaning. Samples are collected in a separate cleaned labeled bottle as stated in Table 39.4.4.

39.4.5 Test Functions

a. *Visual inspection:* The pre- and postvisual inspection of filtration assembly and filling machine parts is performed as per Attachment VIII. The cleaning validation officer will visualize the equipment's outer and inner surfaces (difficult and not difficult to clean) to verify that the surfaces are free from any kind of visibly detectable residue.

b. *pH determination:* pH determination of the final rinse should be performed as per STM No. PL-0021.

c. *Conductivity:* The test for conductivity of the final rinse should be performed as per SOP No. QCE-034.

Your Company's Logo

Your Company's Name

TABLE 39.4.4

Sampling Volume

S. No.	Test	Sample Quantity (mL)	Total Quantity (mL)	Sampling Bottle	Identification Labeling	Testing Requirements
1	pH	100	100	Clean bottle	R1-pH	Analyze the samples after collection within 2 h
2	Conductivity	100	100	Clean bottle	R1-conductivity	Analyze the samples after collection within 2 h
3	TOC	50	100	Clean bottle	R1-TOC	Analyze the samples after collection within 2 h
4	MAC	50	50	Clean bottle	R1-MAC	Analyze the samples after collection within 24 h
5	Bio-burden	100	100	Sterilized bottle	R1-BB	Analyze the samples after collection within 4 h
6	Endotoxin	10		De-pyrogenated bottle	R1-endotoxin	Analyze the samples after collection within 24 h

d. *Total organic carbon:* The test for TOC of the final rinse should be performed as per SOP No. QCE-078.

e. *Maximum allowable carryover:* The test for MAC of the final rinse/swab is performed as per the following validated method for cleaning validation.

f. *Bio-burden test:* The test for bio-burden is performed as per STM No. MC-0001 and SOP No. ABC-0005 by the QC Microbiology section.

g. *Endotoxin test:* This test is performed as per STM No. MC-0002 by the QC Microbiology section.

i. *Swab sampling recovery challenge test:* The recovery challenge test should be performed for the swab sample.

39.4.5.1 Vancomycin HCl

Technique HPLC

STM No. HP-0139

39.4.5.2 Bacitracin Injection, USP

Technique HPLC

STM No. HP-0475

Your Company's Logo **Your Company's Name**

Note:

- Analysis of swab samples is performed by pooling the 10 mL swab extraction as required for specific analysis

39.4.6 Verification of Documents

a. Verify the cleaning procedure.
b. Verify the CIP cycle printout.
c. Verify the cleaning logbook records.
d. Verify the staff training record.

39.4.7 Documentation

a. Printout of the CIP cycle.
b. All analysis results are recorded in the analysis logbook.
c. Printouts and chromatograms are attached to the validation report and a copy of that is also attached to the analytical logbook.
d. All analysis and data should be verified by the second analyst.
e. The cleaning validation officer checks all training records.
f. The final report for cleaning validation should be prepared by the cleaning validation officer and subsequently reviewed and approved as per the procedure.

39.4.8 Acceptance Criteria

The acceptance criteria are based on process validation studies and worst case as mentioned in the injectable products matrix.

a. *Visual inspection:* The visible internal equipment surfaces and all critical and difficult-to-clean parts are optically free from residue and the color of the final rinse water is comparable to WFI.
b. *pH determination:* The pH value of the final rinse should be comparable to the blank WFI sample kept under the same conditions (WFI pH limit 5–7).

Your Company's Logo **Your Company's Name**

c. *Conductivity:* The conductivity of the final rinse should be comparable to the blank WFI sample kept under the same conditions (WFI conductivity limit is 1.3 µs/cm at 25°C).

d. *Total organic carbon:* The TOC of the final rinse should be comparable to the blank WFI sample kept under the same conditions (WFI TOC limit is NMT 500 ppb).

e. *Maximum allowable carryover:* The active ingredient in the final rinse and swabs is either not detected or is equal to or less than the MAC (calculated theoretically for each product).

Based on the "worst-case" concept, the MAC is calculated for each product. For each product, MAC is calculated as follows:

$$\text{MAC} = \frac{\text{TD} \times \text{BS} \times \text{SF}}{\text{LDD}}$$

where MAC is the maximum allowable carryover, TD is a single therapeutic dose, BS is the batch size of the next product to be manufactured in the same equipment, SF is the safety factor, and LDD is the largest daily dose of the next product to be manufactured in the same equipment.

The calculated value will be the maximum amount of active ingredient of a certain product that is allowed to be carried over to the next batch.

f. *Bio-burden:* The bio-burden should not be more than 10 cfu/100 mL for the rinses and not more than 3 cfu/25 cm^2 for the swabs.

g. *Endotoxin:* The endotoxin should not be more than 0.25 EU/mL.

h. *Swab sampling recovery challenge test:* The swab recovery challenge test should be 95–105% of the known concentration of standard spiked.

39.4.9 List of Attachments

Attachment I	Description of equipment and product
Attachment II	Sampling technique
Attachment III	Equipment description and sampling locations
	Figure 39.4.1: Prefiltration assembly
	Figure 39.4.2: Filling needles, pumps, manifold, pre- and post-pump hoses
	Figure 39.4.3: Vibratory sorters, stopper feed track
	Figure 39.4.4: Buffer tank
Attachment IV	Training record verification
Attachment V	Swab sampling and rinse analysis results
Attachment VI	Swab sampling recovery challenge test results

Your Company's Logo **Your Company's Name**

Attachment I

Description of Equipment and Product

Equipment Name: Filtration Assembly/Filling Machine Parts

Capacity: _____

Calibrated on: _____

Location: _____

Room No.: _____

Previous Product: _____

Batch No. of the Product: _____

Manufacturing Date: _____

Active Ingredient: _____

Therapeutic Group: _____

Cleaning Date: _____

Cleaning SOP No.: _____ Revision No.: _____

Sampling Technique: ABC-006

Cleaning Sample Analysis Date/Time: _____ Assay Result: _____

Test Method Reference: _____ Reference Analytical Logbook: _____

Limit of Detection: _____

Next Product to Be Manufactured in the Same Equipment: _____

Safety Factor: _____

Your Company's Logo **Your Company's Name**

Attachment II

Sampling Technique

Product Name: _____

Batch No: _____

Process Involved: _____

Sampling Location/ID	Sampling Criteria		Type of Sample		Sample Area/Quantity	
	D	N	S	R	cm^2	300 mL
R1*		✓		✓		
R2*		✓		✓		
S1*		✓	✓			
S2*		✓	✓			
S3*		✓	✓			
S4*		✓	✓			
S5*		✓	✓			
S6*		✓	✓			
S7*		✓	✓			
S8*		✓	✓			
S9*		✓	✓			
S10*		✓	✓			
S11*		✓	✓			
S12*		✓	✓			
S13*		✓	✓			
S14*		✓	✓			
S15*		✓	✓			
S16*		✓	✓			
S17*		✓	✓			
S18*		✓	✓			
S19*		✓	✓			
S20*		✓	✓			

continued

Your Company's Logo **Your Company's Name**

Sampling Location/ID	Sampling Criteria		Type of Sample		Sample Area/Quantity	
	D	N	S	R	cm^2	300 mL
S21*		✓	✓			
S22*		✓	✓			
S23*		✓	✓			
S24*		✓	✓			
S25*		✓	✓			
S26*		✓	✓			
S27*		✓	✓			

* refer to Attachment III-Figures 39.4.1 through 39.4.4, S: swab, R: rinse, D: difficult to clean, N: normal.
* Surface swab samples each equal to 25 cm^2.
* Rinse samples each equal to 300 mL.

Performed by: _____ Date: _____

Checked by: _____ Date: _____

Your Company's Logo **Your Company's Name**

Attachment III

Equipment Description and Sampling Locations

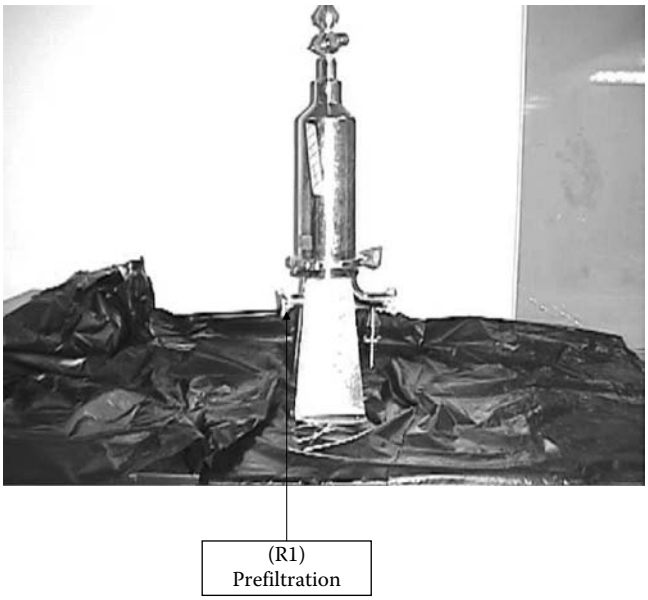


FIGURE 39.4.1
Prefiltration assembly.

Your Company's Logo **Your Company's Name**

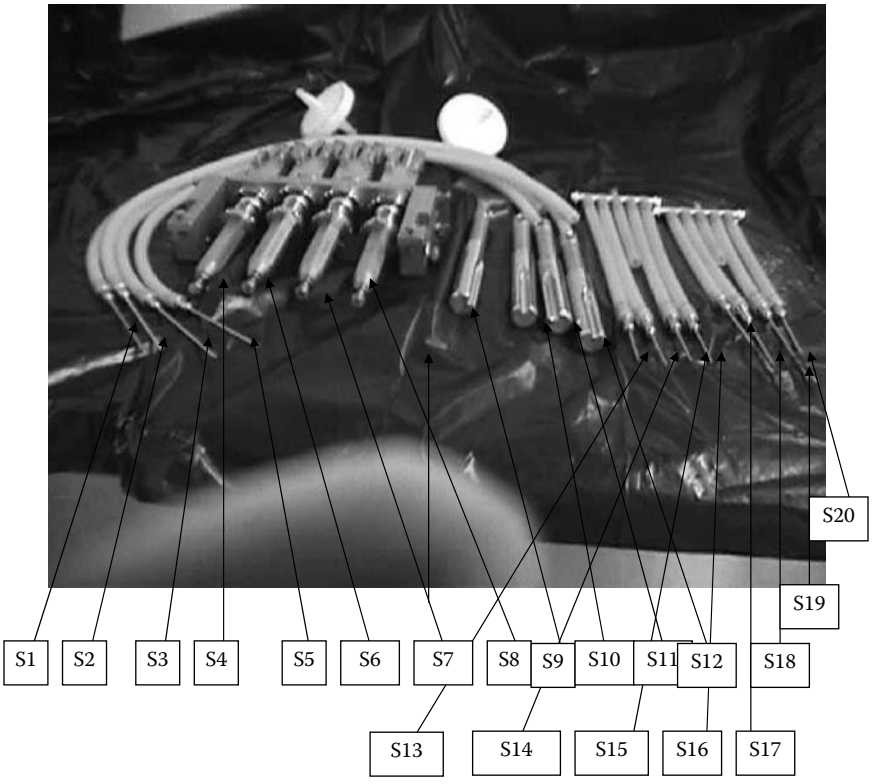


FIGURE 39.4.2
Filling needles, pumps, manifold, pre- and postpump hoses.

Your Company's Logo **Your Company's Name**

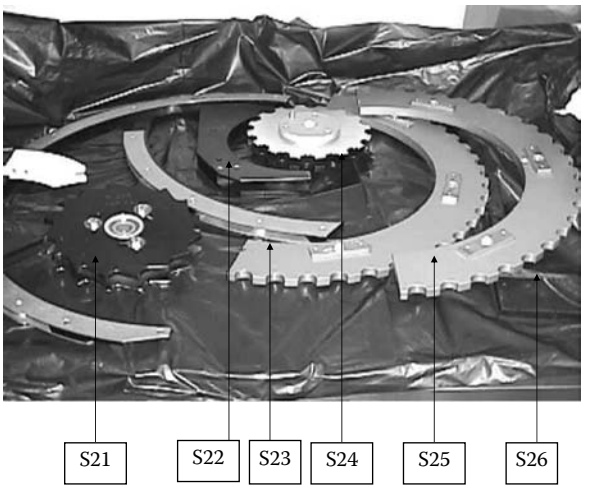


FIGURE 39.4.3
Vibratory sorters, stopper feed track.

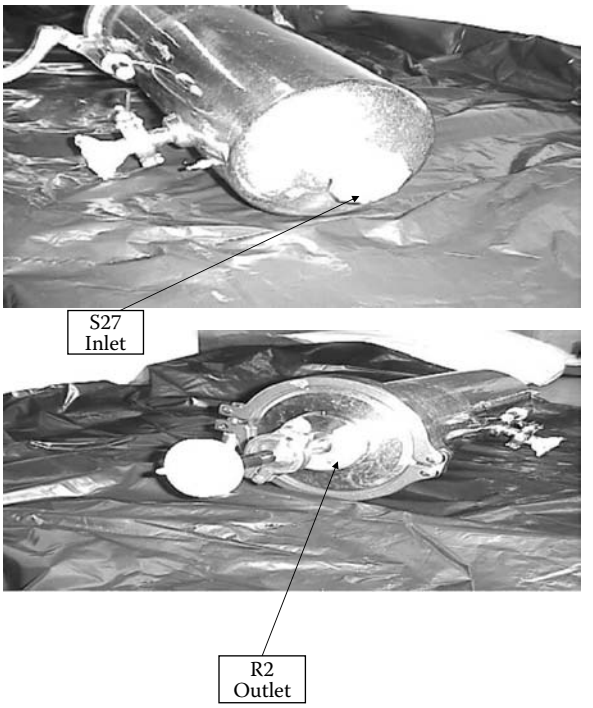


FIGURE 39.4.4
Buffer tank.

Your Company's Logo **Your Company's Name**

Attachment IV

Training Record Verification

The following staff found trained on cleaning of the equipment.

Using SOP No. ABC-007; Revision No; Issued on; Date;

Name: _____ ID: _____

Name: _____ Sign.: _____ Date: _____

Name: _____ ID No.: _____ Sign.: _____ Date: _____

Verified by: _____ Date: _____

Your Company's Logo **Your Company's Name**

Attachment V

Swabs and Rinse Analysis Results

Swab Analysis Results

Sampling Location/ID	Visual Inspection		Carryover HPLC Result per 25 cm^2	Surface Area	Total Carryover
	Pre	Post			
S1					
S2					
S3					
S4					
S5					
S6					
S7					
S8					
S9					
S10					
SI1					
S12					
S13					
S14					
S15					
S16					
S17					
S18					
S19					
S20					
S21					
S22					
S23					
S24					
S25					
S26					
S27					

Pre: before starting the manufacturing of tested batch; post: after the cleaning of tested batch.

Performed by: _____ Date: _____

Checked by: _____ Date: _____

Your Company's Logo **Your Company's Name**

Rinse Analysis Results

Sampling Location	Blank WFI			Sample					
	pH	**Conductivity**	**TOC**	**Total Carryover HPLC Result**	**pH (Limit 5–7)**	**TOC NMT 500 ppb**	**Conductivity NMT 1.3 µs/cm at 25°C**	**Bio-Burden Test NMT 10 cfu/100 mL**	**Endotoxin Test NMT 0.25 EU/mL**
R1									
R2									
R3									

Performed by: _____ Date: _____

Checked by: _____ Date: _____

CLV-39.5

Protocol for Preparation and Holding Vessels for Biological Products

Your Company's Logo

Your Company's Name

ABC Pharmaceutical Company	**CLEANING VALIDATION PROTOCOL** **Equipment Name**	
	Issued on **Date**	**Protocol Number** **CLVL-000**
	Location **Sterile Preparation Area**	

Equipment Name.....**Preparation and Holding Vessels**

Model.....**Model and Number**

Manufacturer.....**Company and country**

39.5.1 Objective

The objective of this protocol is to verify that the cleaning procedure will successfully and consistently reduce the level of traces of residues of the previous product to a predetermined level of acceptability of equipment train and facilities used in the manufacturing and filling of biological products.

39.5.2 Scope

This protocol will cover cleaning of the following tanks:

Formulation tank, FT-01
Formulation tank, FT-02
Mobile holding tank, MT-01
Sterile filling tank, SFT

Your Company's Logo Your Company's Name

39.5.3 Responsibilities

The following personnel are responsible for the execution of this protocol:

The cleaning validation officer is responsible for cleaning validation protocol write up, execution, and report writing.

The production officer and the machine operator are responsible for cleaning the equipment as per the approved procedure.

The QA inspector is responsible for system compliance.

The QC analyst is responsible for performing the analysis of the cleaning samples as per the approved protocol and test method.

39.5.4 Description of the Cleaning Process

The following equipment are cleaned by the CIP procedure as per SOP No. ABC-004:

- Formulation tank, FT-01
- Formulation tank, FT-02
- Mobile holding tank, MT-01
- Sterile filling tank, SFT

39.5.5 Identification of Critical Parameters

The critical parameters are monitored by the online monitoring system as stated in Table 39.5.1.

TABLE 39.5.1

Critical Parameters

Parameters	Specification	Actual Reading
Temperature of DIW water for SFT01-MT01-FT01-FT02	50–60°C	
Pressure SFT01-MT01-FT01-FT02	Minimum 2 bar	
Volume of alkaline cleaning solution SFT01, MT01, FT01	300 kg (L), 150 kg, 100 kg	
Temperature of water for injection	50–60°C	
Conductivity of water rinse	NMT 1.1 µs/cm	
Alkaline solution pH	8.5–11	
Acid solution pH	2.0–5.5	

Your Company's Logo **Your Company's Name**

Critical parameters were set as per the manufacturing guideline of CIP in SOP No. ABC-005 and it is important to follow the set temperature and volume of DIW and WFI to perform cleaning of the formulation tanks.

39.5.6 Documentation

39.5.6.1 Documents Required

a. Equipment cleaning procedure: ABC-001
b. Rinse/swabs sampling procedure: ABC-003
c. Swab recovery challenge test procedure: PDA Guideline
d. Validated method of analysis: HP-002
e. Limit of detection: 2.85 µg/mL

39.5.6.2 Documents Attached/Checking

All analysis results are recorded in the analysis logbook.

Printouts and chromatograms are attached to the validation report and a copy of that is also attached to the analytical logbook.

The cleaning validation officer will check all training records.

The final report for cleaning validation should be prepared by the cleaning validation officer and subsequently reviewed and approved as per the procedure.

39.5.7 Verification of Document

Verify the tanks cleaning procedure.

Verify the CIP cycle printout (if applicable).

Verify the cleaning logbooks.

39.5.8 Test Functions

a. *Visual inspection:* The cleaning validation officer will visualize the equipment's outer and inner surfaces (difficult and not difficult to clean) to verify that the surfaces are free from any kind of visibly detectable residues.

Your Company's Logo **Your Company's Name**

b. *Facility qualification:* Taking swabs for cross-contaminations will perform the test of manufacturing and filling facilities.
c. *pH determination:* pH determination of the final rinse should be performed as per STM No. PL-0021.
d. *Conductivity:* The test for conductivity of the final rinse should be performed as per SOP No. ABC-006.
e. *Total organic carbon:* The test for TOC of the final rinse should be performed as per SOP No. ABC-005.
f. *Maximum allowable carryover:* The test for MAC of the final rinse/swab is performed as per the following validated method for cleaning validation.
g. *Bio-burden test:* The test for bio-burden is performed as per STM No. MC-0001 and SOP No. QC-004 by the QC Microbiology section.
h. *Endotoxin test:* This test should be performed as per STM No. MC-0002 by the QC Microbiology section.
i. *Swab sampling recovery challenge test:* The recovery challenge test should be performed for the swab sample.

39.5.9 Acceptance Criteria

a. *Visual inspection:* The visible internal equipment surfaces and all critical and difficult-to-clean parts are optically free from residue and the color of the final rinse water is comparable to WFI.
b. *Facility qualification:* The floor and wall swabs results should be less than or equal to the MAC of the Insulin 70/30.
c. *pH determination:* The pH value of the final rinse should be comparable to the blank WFI sample kept under the same conditions (WFI pH limit 5–7).
d. *Conductivity:* The conductivity of the final rinse should be comparable to the blank WFI sample kept under the same conditions (WFI conductivity limit is 1.1 µs/cm at 25°C).
e. *Total organic carbon:* The TOC of the final rinse should be comparable to the blank WFI sample kept under the same conditions (WFI TOC limit is NMT 500 ppb).
f. *Active ingredient detection:* The active ingredient in the final rinse/swabs should be either not detected or less than the limit of detection of the biological product, which is XX µg/mL.
g. *Bio-burden:* The bio-burden should not be more than 10 cfu/100 mL for the rinses.
h. *Endotoxin:* The endotoxin should not be more than 0.25 EU/mL.

Your Company's Logo **Your Company's Name**

i. *Swab recovery challenge test:* The swab recovery challenge test should be 70% of the known concentration of the standard spiked.

39.5.10 Description of the Sampling Process

39.5.10.1 Sampling Technique

The sampling and testing are carried out as per the attached sampling and testing plan and figure of the corresponding equipment (Annexure B and figures).

39.5.10.2 Procedure for Sample

The water rinse is collected as per SOP No. ABC-004

The cleaning validation officer is responsible for collecting the sample for water rinses in clean bottles

For the bio-burden test the sample is collected in sterile bottles, and for the endotoxin test the sample is collected in de-pyrogenated bottles

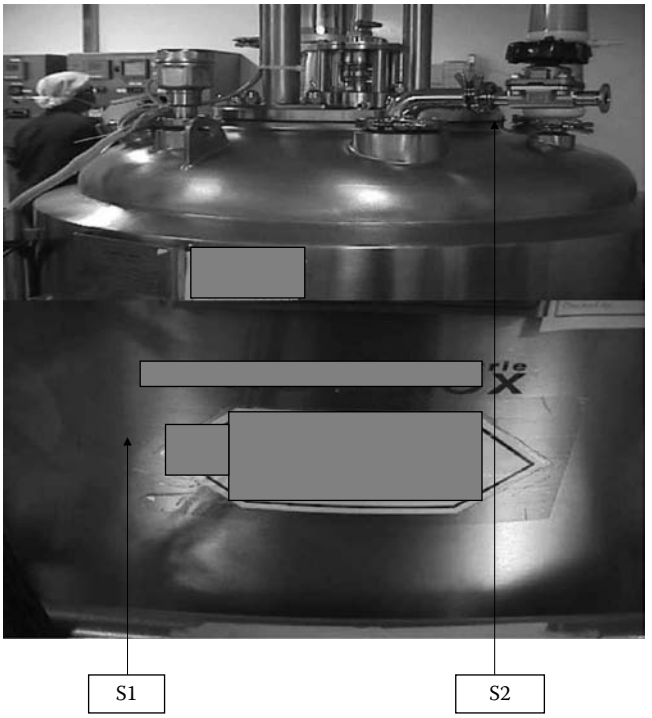


FIGURE 39.5.1
Outer surface preparation vessel (front view).

Your Company's Logo **Your Company's Name**

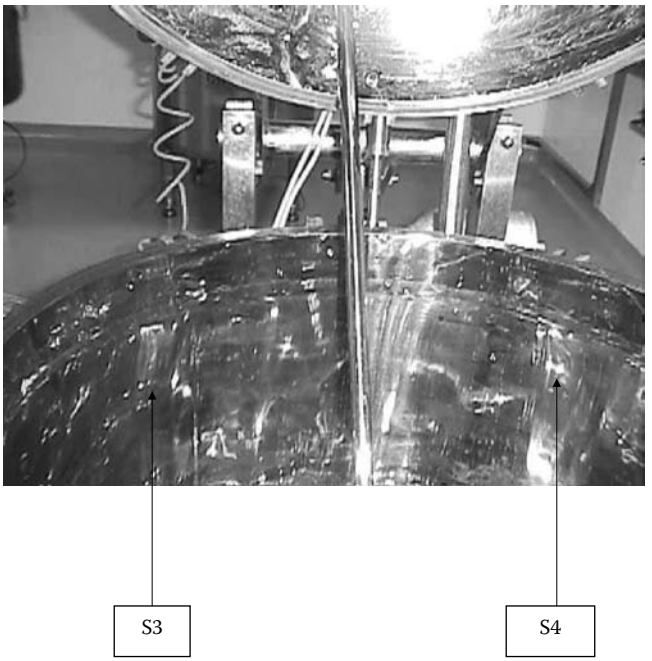


FIGURE 39.5.2
Sampling location inner surface top.

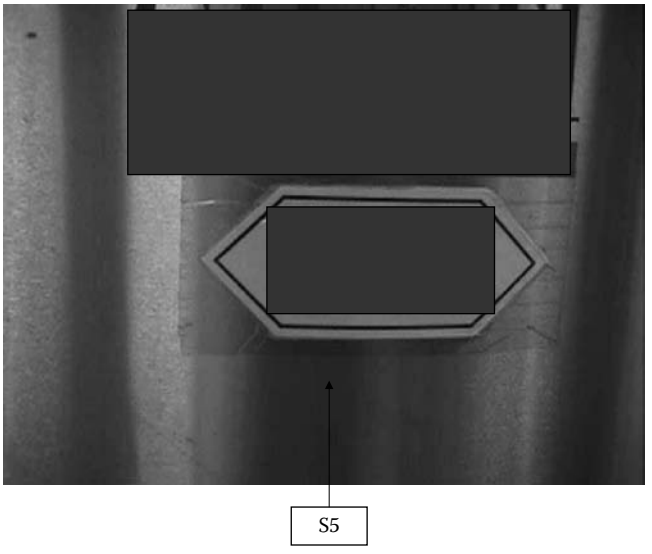


FIGURE 39.5.3
Outer surface (front view).

Your Company's Logo **Your Company's Name**

FIGURE 39.5.4
Outer surface (top).

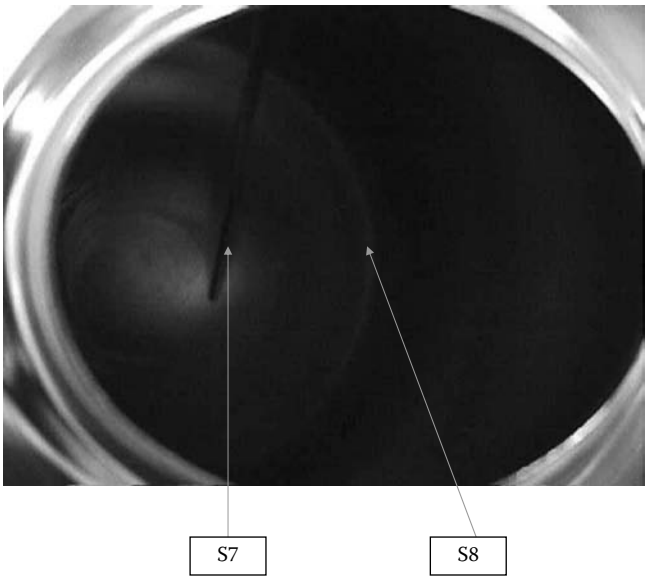


FIGURE 39.5.5
Inner surface, mixer rod.

Your Company's Logo **Your Company's Name**

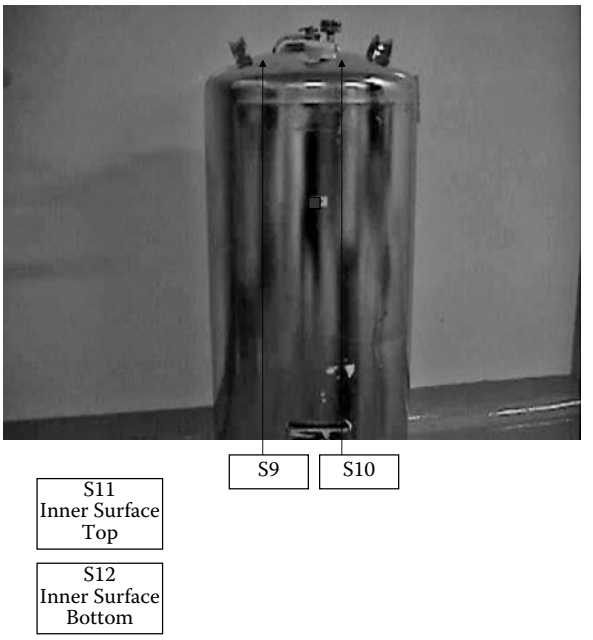


FIGURE 39.5.6
Outer and inner surface.

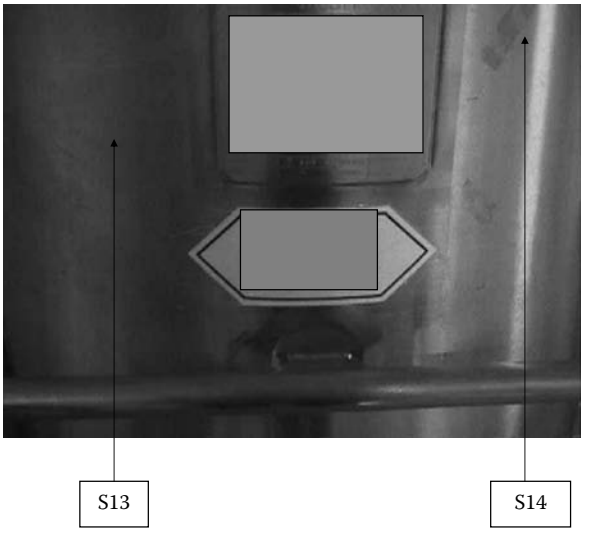


FIGURE 39.5.7
Outer surface.

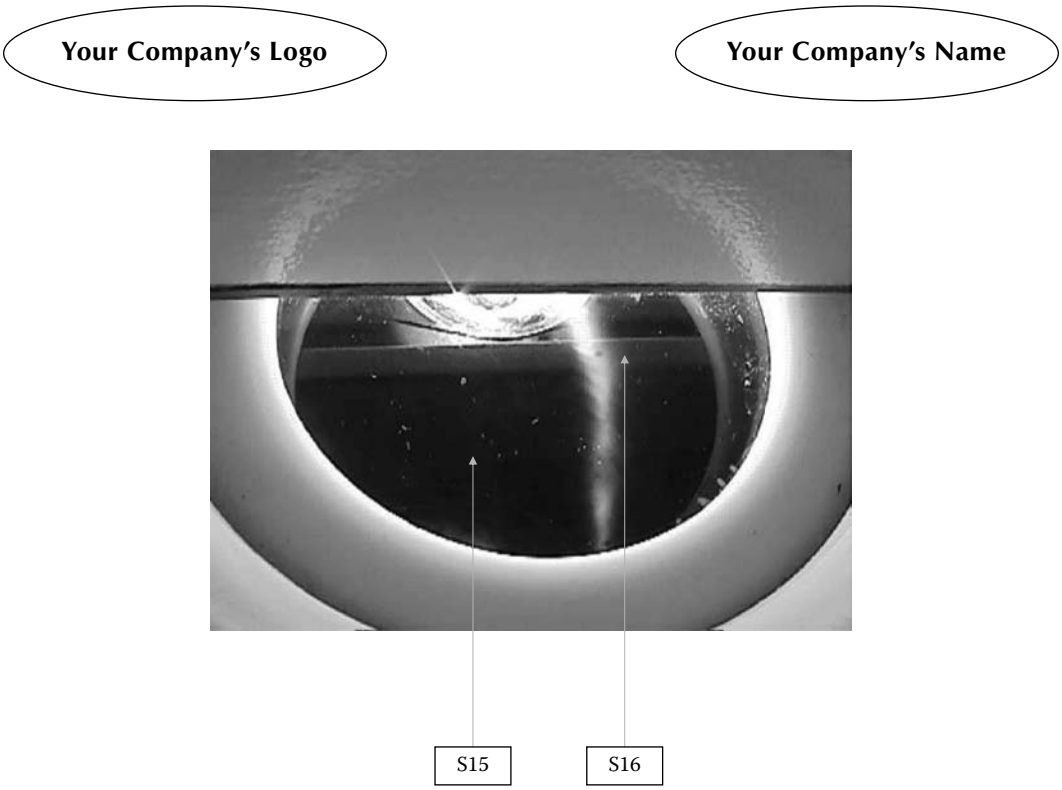


FIGURE 39.5.8
Inner side walls of the vessel.

39.5.10.3 Surface Swabs

Samples of the internal surfaces are taken by moistening the swab (ready-made sterile cotton swab) with a suitable solvent (water for injection)

Sample a 250-cm^2 area and place the swab in a test tube containing 10 mL of solvent (water for injection)

39.5.10.4 Sampling Precautions

Before taking the sample, wear the following:

i. Heat-resistant gloves
ii. Safety goggles

Open the tank outlet valve slowly and collect the sample in labeled bottles as stated in Table 39.5.1.

Your Company's Logo **Your Company's Name**

Annexure A

Equipment used in three strengths of biological products

Formulation tank, FT-01
Formulation tank, FT-02
Mobile holding tank, MT-01
Sterile filling tank, SFT

Annexure B

Sampling and testing plan (formulation tank FT-01)

S. No.	Test	Identification Labeling	Sample Volume (mL)	Sampling Bottle	Testing Specifications	Testing Method/ Procedure No.
1	pH	RFT01-1	100	Clean bottle	5–7 pH unit	STM-PL-001
2	Conductivity				NMT 1.1 µs/cm	
3	TOC				NMT 500 ppb	SOP-ABC-004
4	Biological product				Not detected/less than the limit of detection 2.85 µg/mL	HP-001/V
5	Bio-burden	RFT01-2	100	Sterilized bottle	NMT 10 cfu/100 mL	STM-MC-001
6	Endotoxin	RFT01-3	100	De-pyrogenated bottle	0.25 EU/mL	*MC-002*

RFT01, rinse formulation tank.

Performed by: _____ Date: _____

Checked by: _____ Date: _____

FT-01: Swab formulation tank

Test	Identification Labeling	Equipment Surface	Sample Area	Testing Specifications	Testing Method/ Procedure No.
Insulin	S5	Outer surface 1	25 cm^2	Less than or equal to the limit of detection of insulin	HP-001/V
	S6	Outer surface 2			
	S7	Inner surface 1			
	S8	Inner surface 2			

Performed by: _____ Date: _____

Checked by: _____ Date: _____

Your Company's Logo **Your Company's Name**

Annexure B

Sampling and testing plan (formulation tank FT-02)

S. No.	Test	Identification Labeling	Sample Volume (mL)	Sampling Bottle	Testing Specifications	Testing Method/ Procedure No.
1	pH	RFT02-1	100	Clean bottle	5–7 pH unit	STM-PL-001
2	Conductivity				NMT 1.1 µs/cm	
3	TOC				NMT 500 ppb	SOP-ABC-004
4	Biological product				Not detected/less than the limit of detection (2.85 µg/mL)	HP-001/V
5	Bio-burden	RFT02-2	100	Sterilized bottle	NMT 10 cfu/100 mL	STM-MC-0001
6	Endotoxin	RFT02-3	100	De-pyrogenated bottle	0.25 EU/mL	MC-0002

RFT02, rinse formulation tank.

Performed by: _____ Date: _____

Checked by: _____ Date: _____

FT02: Swab formulation tank

Test	Identification Labeling	Equipment Surface	Sample Area	Testing Specifications	Testing Method/ Procedure No.
Biological product	S9	Outer surface 1	25 cm^2	Not detected/less than the limit of detection (2.85 µg/mL)	HP-001/V
	S10	Outer surface 2			
	S11	Inner surface 1			
	S12	Inner surface 2			

Performed by: _____ Date: _____

Checked by: _____ Date: _____

Your Company's Logo **Your Company's Name**

Annexure B

Sampling and testing plan (mobile holding tank MT-01)

S. No.	Test	Identification Labeling	Sample Volume (mL)	Sampling Bottle	Testing Specifications	Testing Method/ Procedure No.
1	pH	RMT-1	100	Clean bottle	5–7 pH unit	STM-PL-001
2	Conductivity				NMT 1.1 µs/cm	
3	TOC				NMT 500 ppb	SOP-ABC-004
4	Biological product				Not detected/less than the limit of detection (2.85 µg/mL)	*HP-001/V*
5	Bio-burden	RMT-2	100	Sterilized bottle	NMT 10 cfu/100 mL	STM-MC-001
6	Endotoxin	RMT-3	100	De-pyrogenated bottle	0.25 EU/mL	*MC-002*

RMT-1, rinse mobile holding tank.

Performed by: _____ Date: _____

Checked by: _____ Date: _____

MT-01: Swab mobile tank

Test	Identification Labeling	Equipment Surface	Sample Area	Testing Specifications	Testing Method/ Procedure No.
Biological product	S13	Outer surface 1	25 cm^2	Not detected/less than the limit of detection (2.85 µg/mL)	HP-001/V
	S14	Outer surface 2			
	S15	Inner surface 1			
	S16	Inner surface 2			

Performed by: _____ Date: _____

Checked by: _____ Date: _____

Your Company's Logo **Your Company's Name**

Annexure B

Sampling and testing plan (sterile filling tank SFT)

No	Test	Identification Labeling	Sample Volume (mL)	Sampling Bottle	Testing Specifications	Testing Method/ Procedure No.
1	pH	RSFT-1	100	Clean bottle	5–7 pH unit	STM-PL-001
2	Conductivity				NMT 1.1 µs/cm	
3	TOC				NMT 500 ppb	SOP-ABC-004
4	Biological product				Not detected/less than the limit of detection (2.85 µg/mL)	HP-001/V
5	Bio-burden	RSFT-2	100	Sterilized bottle	NMT 10 cfu/100 mL	STM-MC-001
6	Endotoxin	RSFT-3	100	De-pyrogenated bottle	0.25 EU/mL	*MC-002*

SFT-1, rinse sterile filling tank.

Performed by: _____ Date: _____

Checked by: _____ Date: _____

SFT: Swab sterile filling tank

Test	Identification Labeling	Equipment Surface	Sample Area	Testing Specifications	Testing Method/ Procedure No.
Biological product	S1	Outer surface 1	25 cm^2	Not detected/less than the limit of detection (2.85 µg/mL)	HP-001/V
	S2	Outer surface 2			
	S3	Inner surface 1			
	S4	Inner surface 2			

Performed by: _____ Date: _____

Checked by: _____ Date: _____

Your Company's Logo **Your Company's Name**

Facility swab sampling

Room No.	Identification Labeling	Facility	Sample Area	Testing Specifications	Testing Method/ Procedure No.
C-19/1	S17	Floor	25 cm^2	Less than or equal to the limit of detection of biological product	HP-001/V
C-19/2	S18	Floor			
C-31	S19	Floor			
C-25	S20	Floor			

Performed by: _____ Date: _____

Checked by: _____ Date: _____

Your Company's Logo **Your Company's Name**

Attachment I

Description of Equipment and Product

Equipment Name: _____

Serial No.: _____

Capacity: _____

Location: _____

Room No.: _____

Previous Product: _____

Batch No. of the Product: _____

Manufacturing Date: _____

Active Ingredient: _____

Therapeutic Group: _____

Cleaning Date: _____

Cleaning SOP No.: _____ Revision No.: _____

Sampling Technique: _____

Cleaning Sample Analysis Date/Time: _____ Assay Result.: _____

Test Method Reference: _____ Reference Analytical Logbook: _____

Limit of Detection: _____

Next Product to Be Manufactured in the Same Equipment: _____

Safety Factor: _____

Your Company's Logo

Your Company's Name

Attachment IIa

Rinse Analysis Results (Sterile Filling Tank)

Sampling Identification	Blank WFI			Sample					
	pH	Conductivity	TOC	Active Ingredient Detection	pH (Limit 5–7)	TOC NMT 500 ppb	Conductivity NMT 1.1 µs/cm at 25°C	Bio-Burden Test NMT 10 cfu/100 mL	Endotoxin Test NMT 0.25 EU/mL
RSFT-1									
RSFT-2									
RSFT-3									

Your Company's Logo **Your Company's Name**

Attachment IIb

Swab Analysis Results (Sterile Filling Tank)

Swab ID	Visual Inspection	Carryover HPLC Results per 25 cm^2	Total Carryover
S1			
S2			
S3			
S4			

The HPLC chromatogram printout should be attached to the analytical logbook.

Performed by: _____ Date _____

Checked by: _____ Date _____

Your Company's Logo

Your Company's Name

Attachment IIc

Rinse Analysis Results (Formulation Tank, FT-01)

Sampling Identification	Blank WFI			Sample					
	pH	Conductivity	TOC	Active Ingredient Detection	pH (Limit 5–7)	TOC NMT 500 ppb	Conductivity NMT 1.1 µs/cm at 25°C	Bio-Burden Test NMT 10 cfu/100 mL	Endotoxin Test NMT 0.25 EU/mL
RFT01-1									
RFT01-2									
RFT01-3									

Your Company's Logo **Your Company's Name**

Attachment IId

Swab Analysis Results (Formulation Tank, FT-01)

Swab ID	Visual Inspection	Carryover HPLC Results per 25 cm^2	Total Carryover
S5			
S6			
S7			
S8			

The HPLC chromatogram printout should be attached to the analytical logbook.

Performed by: _____ Date _____

Checked by: _____ Date _____

Your Company's Logo

Your Company's Name

Attachment IIe

Rinse Analysis Results (Formulation Tank, FT-02)

Sampling Identification	Blank WFI			Sample					
	pH	Conductivity	TOC	Active Ingredient Detection	pH (Limit 5–7)	TOC NMT 500 ppb	Conductivity NMT 1.1 µs/cm at 25°C	Bio-Burden Test NMT 10 cfu/100 mL	Endotoxin Test NMT 0.25 EU/mL
RFT02-1									
RFT02-2									
RFT02-3									

Your Company's Logo **Your Company's Name**

Attachment IIf

Rinse Analysis Results (Formulation Tank, FT-02)

Swab ID	Visual Inspection	Carryover HPLC Results per 25 cm^2	Total Carryover
S9			
S10			
S11			
S12			

The HPLC chromatogram printout should be attached to the analytical logbook.

Performed by: _____ Date _____

Checked by: _____ Date _____

Your Company's Logo

Your Company's Name

Attachment IIg

Rinse Analysis Results (Mobile Holding Tank, MT-01)

Sampling Identification	Blank WFI			Sample					
	pH	Conductivity	TOC	Active Ingredient Detection	pH (Limit 5–7)	TOC NMT 500 ppb	Conductivity NMT 1.1 µs/cm at 25°C	Bio-Burden Test NMT 10 cfu/100 mL	Endotoxin Test NMT 0.25 EU/mL
RMT-1									
RMT-2									
RMT-3									

Your Company's Logo **Your Company's Name**

Attachment IIh

Swab Analysis Results (Mobile Holding Tank, MT-01)

Swab ID	Visual Inspection	Carryover HPLC Results per 25 cm^2	Total Carryover
S13			
S14			
S15			
S16			

The HPLC chromatogram printout should be attached to the analytical logbook.

Performed by: _____ Date _____

Checked by: _____ Date _____

CLV-39.6

Protocol for Filtration Assembly and Filling Machine for Biological Products

Your Company's Logo **Your Company's Name**

ABC Pharmaceutical Company	**CLEANING VALIDATION PROTOCOL** **Equipment Name**	
	Issued on **Date**	**Protocol Number** **CLVL-000**
	Location **Sterile Preparation Area**	

Equipment Name.....**Filtration Assembly and Filling Machine for Biological Products**

Model.....**Model and Number**

Manufacturer .....**Company and country**

39.6.1 Objective

The objective of this protocol is to verify that the cleaning procedure will successfully and consistently reduce the level of residues of biological product to a predetermined level of acceptability for the filtration assembly and vial filling machine parts.

39.6.2 Scope

This protocol will cover cleaning of the filtration assembly and vial filling machine parts for biological products.

Your Company's Logo

Your Company's Name

39.6.3 Cleaning Verification Approach

The filling machine (filling machine parts and filtration assembly) is cleaned manually as per SOP No. ABC-001. Filling machine parts are dismantled and washed separately. At the end of cleaning, the parts are assembled together and connected with a hose. A final rinse is then collected from the filling machine manifold and filling nozzles as shown in the sampling and testing plan and figures (Figures 39.6.1 through 39.6.3).

39.6.4 Responsibilities

The following personnel are responsible for the execution of this protocol:

- The cleaning validation officer is responsible for cleaning validation protocol write up, execution, and report writing.
- The production officer and the machine operator are responsible for cleaning the equipment as per the approved procedure.
- The QA inspector is responsible for system compliance.
- The QC analyst is responsible for performing analysis of the cleaning samples as per the approved protocol and test method.

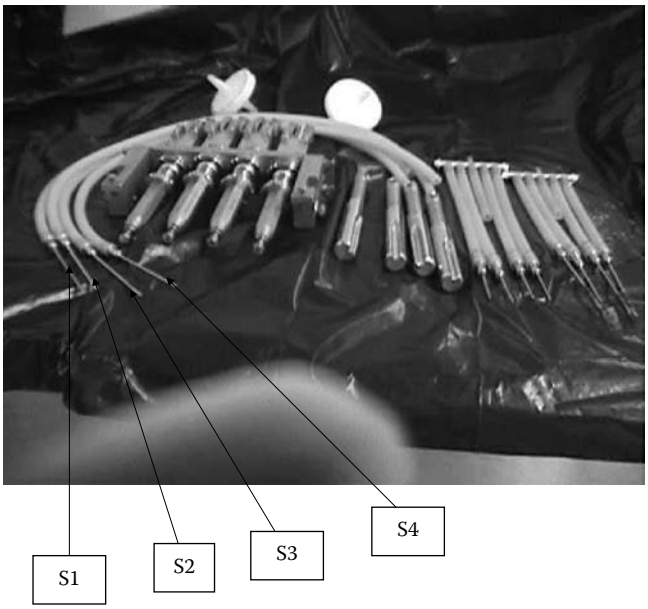


FIGURE 39.6.1
Filling needles.

Your Company's Logo **Your Company's Name**

FIGURE 39.6.2
Post filter.

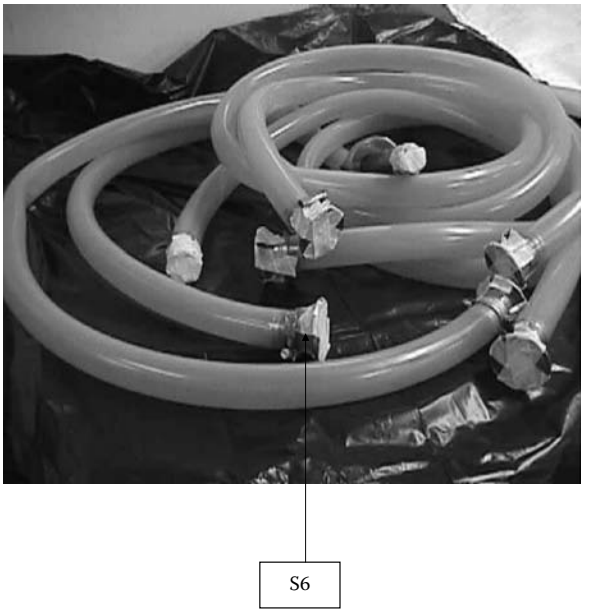


FIGURE 39.6.3
Tubing.

Your Company's Logo

Your Company's Name

39.6.5 Description of the Cleaning Process

Filtration assembly and vial filling machine parts are cleaned manually as per procedure ABC-002.

39.6.6 Documentation

39.6.6.1 Documents Required

a. Equipment cleaning procedure: ABC-001
b. Rinse/swabs sampling procedure: ABC-001
c. Swab recovery challenge test procedure: PDA Guideline
d. Validated method of analysis: HP-001/V
e. Limit of detection: 2.85 µg/mL

39.6.6.2 Documents Attached/Checking

All analysis results are recorded in the analysis logbook.

Printouts and chromatograms are attached to the validation report and a copy of that is also attached to the analytical logbook.

The cleaning validation officer will check all training records.

The final report for cleaning validation is prepared by the cleaning validation officer and subsequently reviewed and approved as per the procedure.

39.6.7 Verification of Documents

Verify the filtration assembly and filling machine parts cleaning procedure.

Verify the filtration assembly and filling machine parts cleaning logbook records.

39.6.8 Test Functions

a. *Visual inspection:* The visual inspection of filtration assembly and filling machine parts should be performed.

The cleaning validation officer will visualize the equipment's outer and inner surfaces (difficult and not difficult to clean) to verify that the surfaces are free from any kind of visibly detectable residue.

b. *Facility qualification:* Test for cross-contamination of manufacturing and filling facilities will be performed by taking swabs.
c. *pH determination:* pH determination of the final rinse should be performed as per the standard test method (STM PL-001).
d. *Conductivity:* The test for conductivity of the final rinse should be performed as per SOP No. ABC-003.
e. *Total organic carbon:* The test for TOC of the final rinse should be performed as per SOP No. QC-001.
f. *Maximum allowable carryover:* The test for MAC of the final rinse/swab is performed as per the following validated method for cleaning validation.
g. *Bio-burden test:* The test for bio-burden is performed as per STM No. MC-001 and SOP No. QC-002 by the QC Microbiology section.
h. *Endotoxin test:* This test should be performed as per the standard test method MC-002 by the QC Microbiology section.
i. *Swab sampling recovery challenge test:* The recovery challenge test should be performed for the swab sample.

39.6.9 Acceptance Criteria

a. *Visual inspection:* The visible internal equipment surfaces and all critical and difficult-to-clean parts are optically free from residue and the color of the final rinse water is comparable to WFI.
b. *Facility qualification:* The floor and wall swabs results should be less than or equal to the MAC of the biological products.
c. *pH Determination:* The pH value of the final rinse should be comparable to the blank WFI sample kept under the same conditions (WFI pH limit 5–7).
d. *Conductivity:* The conductivity of the final rinse should be comparable to the blank WFI sample kept under the same conditions (WFI conductivity limit is 1.1 µs/cm at 25°C).
e. *Total organic carbon:* The TOC of the final rinse should be comparable to the blank WFI sample kept under the same conditions (WFI TOC limit is NMT 500 ppb).
f. *Active ingredient detection:* The active ingredient in the final rinse/swabs should be either not detected or less than the limit of detection of the biological product, which is XX µg/mL.

Your Company's Logo **Your Company's Name**

g. *Bio-burden:* The bio-burden should not be more than 10 cfu/100 mL for the rinses.
h. *Endotoxin:* The endotoxin should not be more than 0.25 EU/mL.
i. *Swab recovery challenge test:* The swab recovery challenge test should be 70% of the known concentration of standard spiked.

39.6.10 Description of the Sampling Process

39.6.10.1 Sampling Technique

The sampling and testing are carried out as per the attached sampling and testing plan.

39.6.10.2 Procedure for Sample

The water rinse is collected as per SOP No. ABC-004.

The cleaning validation officer is responsible for collecting the sample for water rinses in clean bottles.

For the bio-burden test the sample is collected in a sterile bottle, and for the endotoxin test the sample is collected in de-pyrogenated bottles.

39.6.10.3 Sampling Precautions

Before taking the sample, wear the following:

i. Heat-resistant gloves
ii. Safety goggles

Your Company's Logo **Your Company's Name**

Annexure A

Sampling and Testing Plan

Rinses

S. No.	Test	Identification Labeling	Sample Volume (mL)	Sampling Bottle	Testing Specifications	Testing Method/ Procedure No.
1	pH	R1–R6	100	Clean bottle	5–7 pH unit	STM-PL-001
2	Conductivity			Clean bottle	NMT 1.1 µs/cm	
3	TOC			Clean bottle	NMT 500 ppb	SOP-QC-002
4	Biological product			Clean bottle	Not detected/less than the limit of detection (2.77 µg)	Validated HPLC method
5	Bio-burden	R7	100	Sterilized bottle	NMT 10 cfu/100 mL	STM-MC-001
6	Endotoxin	R8	100	De-pyrogenated bottle	0.25 EU/mL	MC-002

R1: filling needle 1, R2: filling needle 2, R3: filling needle 3, R4: filling needle 4, R5: postfilter, R6: rubber, R7: bio-burden (from all parts), R8: endotoxin (from all parts).

Performed by: _____ Date _____

Checked by: _____ Date _____

Your Company's Logo **Your Company's Name**

Annexure A

Sampling and Testing Plan

Swabs

Test	Identification Labeling	Equipment Surface	Sample Area	Testing Specifications	Testing Method/ Procedure No.
Biological product	S1	Filling needle 1	25 cm^2		ABC-005
	S2	Filling needle 2			
	S3	Filling needle 3			
	S4	Filling needle 4			
	S5	Postfilter			
	S6	Rubber			

Performed by: _____ Date _____

Checked by: _____ Date _____

Your Company's Logo **Your Company's Name**

Attachment I

Description of Equipment and Product

Equipment Name: _____

Serial No.: _____

Capacity: _____

Location: _____

Room No.: _____

Previous Product: _____

Batch No. of the Product: _____

Manufacturing Date: _____

Active Ingredient: _____

Therapeutic Group: _____

Cleaning Date: _____

Cleaning SOP No.: _____ Revision No.: _____

Sampling Technique: _____

Cleaning Sample Analysis Date/Time: _____ Result: _____

Test Method Reference: _____ Reference Analytical Logbook: _____

Limit of Detection: _____

Next Product to Be Manufactured in the Same Equipment: _____

Safety Factor: _____

Your Company's Logo **Your Company's Name**

Attachment II

Rinse Analysis Results

Sampling Identification	Blank WFI			Sample					
	pH	Conductivity	TOC	Total Carryover HPLC Result	pH (Limit 5–7)	TOC NMT 500 ppb	Conductivity NMT 1.1 µs/cm at 25°C	Bio-Burden Test NMT 10 cfu/100 mL	Endotoxin Test NMT 0.25 EU/mL
R1									
R2									
R3									
R4									
R5									
R6									
R7									
R8									

The HPLC chromatogram printout should be attached to the analytical logbook.

Performed by: _____ Date _____

Checked by: _____ Date _____

Your Company's Logo **Your Company's Name**

Swab Analysis Results

Swab ID	Visual Inspection	Carryover HPLC Results per 25 cm^2	Total Carryover
S1			
S2			
S3			
S4			
S5			
S6			
S7			
S8			
S9			
S10			

Performed by: _____ Date _____

Checked by: _____ Date _____

CLV-40

Cleaning Validation Tentative Plan (Schedule)

Your Company's Logo

Your Company's Name

A sample plan is given here considering the cleaning validation for solid dosage and some of the liquid dosage forms and related equipment from the matrix. The same template can be used to prepare schedule for all other equipments for other dosage forms.

40.1 Tablets Products

Equipment	Worst-Case Product Name	Batch No.			Quarter-I	Quarter-II	Quarter-III	Quarter-IV
Granulation machine	Ciprofloxacin tablets 500 mg							
	Ketotifen tablets 1.0 mg							
	Diclofenac 50 mg tablets							
	Sulfamethoxazole tablets							
Fluid bed dryer	Ciprofloxacin tablets 500 mg							
	Ketotifen tablets 1.0 mg							
	Diclofenac 50 mg tablets							
	Sulfamethoxazole tablets							
Sieve	Ciprofloxacin tablets 500 mg							
	Ketotifen tablets 1.0 mg							
	Diclofenac 50 mg tablets							
	Sulfamethoxazole tablets							

Your Company's Logo **Your Company's Name**

Equipment	Worst-Case Product Name	Batch No.			Quarter-I	Quarter-II	Quarter-III	Quarter-IV
Powder bins	Ciprofloxacin tablets 500 mg							
	Ketotifen tablets 1.0 mg							
	Diclofenac 50 mg tablets							
	Sulfamethoxazole tablets							
Tablet press A	Ciprofloxacin tablets 500 mg							
	Ketotifen tablets 1.0 mg							
	Diclofenac 50 mg tablets							
	Sulfamethoxazole tablets							
Mixer	Ciprofloxacin tablets 500 mg							
	Ketotifen tablets 1.0 mg							
	Diclofenac 50 mg tablets							
	Sulfamethoxazole tablets							
Cota	Diclofenac 50 mg tablets							
	Sulfamethoxazole tablets							
	Diclofenac 50 mg tablets							
	Sulfamethoxazole tablets							
Tablet press B	Diclofenac 50 mg tablets							
	Sulfamethoxazole tablets							
	Diclofenac 50 mg tablets							
	Sulfamethoxazole tablets							
Tablet press C	Diclofenac 50 mg tablets							
	Sulfamethoxazole tablets							
	Diclofenac 50 mg tablets							
	Sulfamethoxazole tablets							

40.2 Tablets (Coated) Products

Equipment	Worst-Case Product Name	Batch No.			Quarter-I	Quarter-II	Quarter-III	Quarter-IV
Sugar-coating pan	Sennisode 12 mg tablets							
	Bisacodyl 5 mg tablets							
	Ibuprofen 200 mg tablets							

Your Company's Logo

Your Company's Name

40.3 Capsules Products

Equipment	Worst-Case Product Name	Batch No.			Quarter-I	Quarter-II	Quarter-III	Quarter-IV
Encapsulator type A	Oxytetracycline 250 mg capsules							
	Indomethacin 25 mg capsules							
	Fluoxitin 20 mg capsules							
Encapsulator type B	Lansoprazole 30 mg capsules							
	Erythromycin 250 mg capsules							
	Diclofenac 100 mg capsules							
	Ferrous sulfate capsules							

40.4 PPS Products

Equipment	Worst-Case Product Name	Batch No.	Quarter-I	Quarter-II	Quarter-III	Quarter-IV
Granulator A	Erythromycin 200 mg/5 mL					
	Azythromycin 200 mg/5 mL					
Sieve	Erythromycin 200 mg/5 mL					
	Azythromycin 200 mg/5 mL					
PPS filling machine	Erythromycin 200 mg/5 mL					
	Azythromycin 200 mg/5 mL					
Granulator B	Erythromycin 200 mg/5 mL					
	Azythromycin 200 mg/5 mL					

Your Company's Logo

Your Company's Name

40.5 Syrup Products

Equipment	Worst-Case Product Name	Batch No.	Quarter-I	Quarter-II	Quarter-III	Quarter-IV
Manufacturing vessels 01 02 03 04	Multivitamins syrup					
	Promethazine HCl					
	Paracetamol syrup					
Holding tanks 01 02 04 05 06	Multivitamins syrup					
	Promethazine HCl					
	Paracetamol syrup					
Filling lines Type A Type B Type C	Multivitamins syrup					
	Promethazine HCl					
	Paracetamol syrup					

Your Company's Logo

Your Company's Name

40.6 Suspension Products

Equipment	Worst-Case Product Name	Batch No.	Quarter-I	Quarter-II	Quarter-III	Quarter-IV
Manufacturing vessels 05 06	Al–Mg hydroxide					
	Ibuprofen					
	Kaopectate					
Holding tanks 07 08 09	Al–Mg hydroxide					
	Ibuprofen					
	Kaopectate					

Equipment	Worst-Case Product Name	Batch No.	Quarter-I	Quarter-II	Quarter-III	Quarter-IV
Filling lines A, B, and C	Al–Mg hydroxide					
	Ibuprofen					
	Kaopectate					

Your Company's Logo

Your Company's Name

40.7 Drops Products

Equipment	Worst-Case Product Name	Batch No.	Quarter-I	Quarter-II	Quarter-III	Quarter-IV
Manufacturing vessel 07	Multivitamins					
	Ferrous sulfate					
	Oxymetazoline 0.05%					
Holding tanks 10 11	Multivitamins					
	Ferrous sulfate					
	Oxymetazoline 0.05%					
Filling line 05	Multivitamins					
	Ferrous sulfate					
	Oxymetazoline 0.05%					

CLV-41

Cleaning Validation Sampling and Testing Status

Your Company's Logo

Your Company's Name

A template for the updates and status of cleaning validation program is presented here. This template may be used to track the progress and development of each cleaning validation project corresponding to various dosage forms and related equipments.

Equipment	Worst-Case Products	Sample Execution Analysis									Status
		Sample 1			Sample 2			Sample 3			
		Date	*B. No.*	*Analysis*	*Date*	*B. No.*	*Analysis*	*Date*	*B. No.*	*Analysis*	
Manufacturing vessels											
		xx.xx.xx	A1	Completed	xx.xx.xx	B1	Completed	xx.xx.xx	C1	Completed	Report closed
02	Multivitamins										Production plan awaited
03	Promethazine HCl	xx.xx.xx	A1	Completed	xx.xx.xx	B1	Completed	xx.xx.xx	C1	Completed	Report closed
04	Paracetamol										
		xx.xx.xx	A1	Completed	xx.xx.xx	B1	Completed				Interim report available
05	Al–Mg hydroxide	xx.xx.xx	A1	Completed							One sample awaited
06	Ibuprofen Kaopectate	xx.xx.xx	A1	Completed	xx.xx.xx	B1	Completed				Two samples awaited
Holding tanks	Multivitamins	xx.xx.xx	A1	Completed	xx.xx.xx	B1	Completed				Two samples awaited
01	Promethazine HCl	xx.xx.xx	A1	Completed	xx.xx.xx	B1	Completed	xx.xx.xx	C1	Completed	Report closed
02	Paracetamol	xx.xx.xx	A1	Completed	xx.xx.xx	B1	Completed				Two samples awaited
03											
04											
05											
06											

Equipment	Worst-Case Product	Sample Execution Analysis									Status
		Sample 1			Sample 2			Sample 3			
		Date	*B. No.*	*Analysis*	*Date*	*B..No.*	*Analysis*	*Date*	*B. No.*	*Analysis*	
Filling lines											
Line no. 1		xx.xx.xx	A1	Completed	xx.xx.xx	B1	Completed				Two samples
Line no. 2		xx.xx.xx	A1	Completed	xx.xx.xx	B1	Completed	xx.xx.xx	C1	Completed	Report closed
Line no. 3		xx.xx.xx	A1	Completed	xx.xx.xx	B1	Completed				Two samples

CLV-42

Cleaning Validation Regulatory Guidelines

CLV-42.1

*Guide to Inspections Validation of Cleaning Processes**

42.1.1 Introduction

The validation of cleaning procedures has generated considerable discussion since agency documents, including the Inspection Guide for Bulk Pharmaceutical Chemicals and the Biotechnology Inspection Guide, have briefly addressed this issue. These agency documents clearly establish the expectation that cleaning procedures (processes) should be validated.

This guide is designed to establish inspection consistency and uniformity by discussing practices that have been found to be acceptable (or unacceptable). Simultaneously, one must recognize that for cleaning validation, as with the validation of other processes, there may be more than one way of validating a process. In the end, the test of any validation process is whether scientific data show that the system consistently does as expected and produces a result that consistently meets predetermined specifications.

This guide is intended to cover equipment cleaning for chemical residues only.

42.1.2 Background

For FDA to require that equipment should be clean prior to use is nothing new. The 1963 GMP Regulations (Part 133.4) stated that "Equipment *** shall be maintained in a clean and orderly manner ***." A very similar section on equipment cleaning (211.67) was included in the 1978 CGMP regulations. Of course, the main rationale for requiring clean equipment is to prevent contamination or adulteration of drug products. Historically, FDA investigators have looked for gross insanitation due to inadequate cleaning and maintenance of equipment and/or poor dust control systems. Also, historically speaking, FDA was more concerned about the contamination of nonpenicillin drug products with penicillin or the cross-contamination of drug products with potent steroids or hormones. A number of products have been recalled over the past decade due to actual or potential penicillin cross-contamination.

* *Note:* This document is reference material for investigators and other FDA personnel. The document does not bind FDA, and does not confer any rights, privileges, benefits, or immunities for or on any person(s).

One event, which increased FDA's awareness of the potential for cross-contamination due to inadequate procedures, was the 1988 recall of a finished drug product, Cholestyramine Resin USP. The bulk pharmaceutical chemical used to produce the product had become contaminated with low levels of intermediates and degradants from the production of agricultural pesticides. The cross-contamination in that case is believed to have been due to the reuse of recovered solvents. The recovered solvents had been contaminated because of a lack of control over the reuse of solvent drums. Drums that had been used to store recovered solvents from a pesticide production process were later used to store recovered solvents used for the resin manufacturing process. The firm did not have adequate controls over these solvent drums, did not conduct adequate testing of drummed solvents, and did not have validated cleaning procedures for the drums.

Some shipments of this pesticide-contaminated bulk pharmaceutical were supplied to a second facility at a different location for finishing. This resulted in contamination of the bags used in that facility's fluid bed dryers with pesticide contamination. This in turn led to cross-contamination of lots produced at that site, a site where no pesticides were normally produced.

FDA instituted an import alert in 1992 on a foreign bulk pharmaceutical manufacturer, which manufactured potent steroid products as well as nonsteroidal products using common equipment. This firm was a multiuse bulk pharmaceutical facility. FDA considered the potential for cross-contamination to be significant and to pose a serious health risk to the public. The firm had only recently started a cleaning validation program at the time of the inspection and it was considered inadequate by the FDA. One of the reasons why it was considered inadequate was that the firm was only looking for evidence of the absence of the previous compound. The firm had evidence, from TLC tests on the rinse water, of the presence of residues of reaction by-products and degradants from the previous process.

42.1.3 General Requirements

FDA expects firms to have written procedures (SOPs) detailing the cleaning processes used for various pieces of equipment. If firms have one cleaning process for cleaning between different batches of the same product and use a different process for cleaning between product changes, we expect the written procedures to address these different scenarios. Similarly, if firms have one process for removing water-soluble residues and another process for non-water-soluble residues, the written procedure should address both scenarios and make it clear when a given procedure is to be followed. Bulk pharmaceutical firms may decide to dedicate certain equipment for certain chemical manufacturing process steps that produce tarry or gummy residues that are difficult to remove from the equipment. Fluid bed dryer bags are another example of equipment that is difficult to clean and is often dedicated to a specific product. Any residues from the cleaning process itself (detergents, solvents, etc.) also have to be removed from the equipment.

FDA expects firms to have written general procedures on how cleaning processes will be validated.

FDA expects the general validation procedures to address who is responsible for performing and approving the validation study, the acceptance criteria, and when revalidation will be required.

FDA expects firms to prepare specific written validation protocols in advance for the studies to be performed on each manufacturing system or piece of equipment, which should address such issues as sampling procedures, and analytical methods to be used, including the sensitivity of those methods.

FDA expects firms to conduct the validation studies in accordance with the protocols and to document the results of those studies.

FDA expects a final validation report, which management approves and which states whether or not the cleaning process is valid. The data should support a conclusion that residues have been reduced to an "acceptable level."

42.1.4 Evaluation of Cleaning Validation

The first step is to focus on the objective of the validation process, and we have seen that some companies have failed to develop such objectives. It is not unusual to see manufacturers use extensive sampling and testing programs following the cleaning process without ever really evaluating the effectiveness of the steps used to clean the equipment. Several questions need to be addressed when evaluating the cleaning process. For example, at what point does a piece of equipment or system become clean? Does it have to be scrubbed by hand? What is accomplished by hand scrubbing rather than just a solvent wash? How variable are manual cleaning processes from batch to batch and product to product? The answers to these questions are obviously important to the inspection and evaluation of the cleaning process since one must determine the overall effectiveness of the process. Answers to these questions may also identify steps that can be eliminated for more effective measures and result in resource savings for the company.

Determine the number of cleaning processes for each piece of equipment. Ideally, a piece of equipment or system will have one process for cleaning; however, this will depend on the products being produced and whether the cleanup occurs between batches of the same product (as in a large campaign) or between batches of different products. When the cleaning process is used only between batches of the same product (or different lots of the same intermediate in a bulk process), the firm needs to only meet a criterion of, "visibly clean" for the equipment. Such between-batch cleaning processes do not require validation.

42.1.4.1 Equipment Design

Examine the design of equipment, particularly in those large systems that may employ semiautomatic or fully automatic CIP systems since they represent significant concern. For example, sanitary-type piping without ball valves should be used. When such nonsanitary ball valves are used, as is common in the bulk drug industry, the cleaning process is more difficult.

When such systems are identified, it is important that operators performing cleaning operations are aware of problems and have special training in cleaning these systems and valves. Determine whether the cleaning operators have knowledge of these systems and the level of training and experience in cleaning these systems. Also check the written and validated cleaning process to determine if these systems have been properly identified and validated.

In larger systems, such as those employing long transfer lines or piping, check the flowcharts and piping diagrams for the identification of valves and written cleaning procedures. Piping and valves should be tagged and easily identifiable by the operator performing the cleaning function. Sometimes, inadequately identified valves, both on prints and physically, have led to incorrect cleaning practices.

Always check for the presence of an often-critical element in the documentation of the cleaning processes: identifying and controlling the length of time between the end of processing and each cleaning step. This is especially important for topicals, suspensions, and bulk drug operations. In such operations, the drying of residues will directly affect the efficiency of a cleaning process.

Whether or not CIP systems are used for the cleaning of processing equipment, microbiological aspects of equipment cleaning should be considered. This consists largely of preventive measures rather than removal of contamination once it has occurred. There should be some evidence that routine cleaning and storage of equipment does not allow microbial proliferation. For example, equipment should be dried before storage, and under no circumstances should stagnant water be allowed to remain in equipment subsequent to cleaning operations.

Subsequent to the cleaning process, equipment may be subjected to sterilization or sanitization procedures where such equipment is used for sterile processing, or for nonsterile processing where the products may support microbial growth. While such sterilization or sanitization procedures are beyond the scope of this guide, it is important to note that the control of bio-burden through adequate cleaning and storage of equipment is important to ensure that subsequent sterilization or sanitization procedures achieve the necessary assurance of sterility. This is also particularly important from the standpoint of the control of pyrogens in sterile processing since equipment sterilization processes may not be adequate to achieve significant inactivation or removal of pyrogens.

42.1.4.2 Cleaning Process Written

42.1.4.2.1 Procedure and Documentation

Examine the detail and specificity of the procedure for the (cleaning) process being validated, and the amount of documentation required. We have seen general SOPs, while others use a batch record or logsheet system that requires some type of specific documentation for performing each step. Depending on the complexity of the system and cleaning process and the ability and training of operators, the amount of documentation necessary for executing various cleaning steps or procedures will vary.

When more complex cleaning procedures are required, it is important to document the critical cleaning steps (e.g., certain bulk drug synthesis processes). In this regard, specific documentation on the equipment itself, which includes information about who cleaned it and when, is valuable. However, for relatively simple cleaning operations, the mere documentation that the overall cleaning process was performed might be sufficient.

Other factors such as history of cleaning, residue levels found after cleaning, and variability of test results may also dictate the amount of documentation required. For example, when variable residue levels are detected following cleaning, particularly for a process that is believed to be acceptable, one must establish the effectiveness of the process and operator performance. Appropriate evaluations must be made, and when operator performance is deemed a problem, more extensive documentation (guidance) and training may be required.

42.1.4.3 Analytical Methods

Determine the specificity and sensitivity of the analytical method used to detect residuals or contaminants. With advances in analytical technology, residues from the manufacturing and cleaning processes can be detected at very low levels. If levels of contamination or residue are not detected, this does not mean that there is no residual contaminant present after cleaning. It only means that levels of contaminant greater than the sensitivity or detection limit of the analytical method are not present in the sample. The firm should challenge the analytical method in combination with the sampling method(s) used to show that contaminants can be recovered from the equipment surface and at what level, that is, 50% recovery, 90%, and so on. This is necessary before any conclusions can be made based on the sample results. A negative test may also be the result of a poor sampling technique (see below).

42.1.4.4 Sampling

There are two general types of sampling that have been found to be acceptable. The most desirable is the direct method of sampling the surface of the equipment. Another method is the use of rinse solutions.

a. *Direct surface sampling*: Determine the type of sampling material used and its impact on the test data since the sampling material may interfere with the test. For example, the adhesive used in swabs has been found to interfere with the analysis of samples. Therefore, early in the validation program, it is important to ensure that the sampling medium and solvent (used for extraction from the medium) are satisfactory and can be readily used.

   The advantages of direct sampling are that areas hardest to clean and that are reasonably accessible can be evaluated, leading to establishing a level of contamination or residue per given surface area. Additionally, residues that are "dried out" or are insoluble can be sampled by physical removal.

b. *Rinse samples*: Two advantages of using rinse samples are that a larger surface area may be sampled, and inaccessible systems or ones that cannot be routinely disassembled can be sampled and evaluated.

   A disadvantage of rinse samples is that the residue or contaminant may not be soluble or may be physically occluded in the equipment. An analogy that can be used is the "dirty pot." In the evaluation of cleaning of a dirty pot, particularly with dried-out residue, one does not look at the rinse water to see that it is clean; one looks at the pot.

   Check to see that a direct measurement of the residue or contaminant has been made for the rinse water when it is used to validate the cleaning process. For example, it is not acceptable to simply test rinse water for water quality (does it meet the compendia tests) rather than test it for potential contaminants.

c. *Routine production in-process control monitoring*: Indirect testing, such as conductivity testing, may be of some value for routine monitoring once a cleaning process has been validated. This would be particularly true for the bulk drug substance manufacturer where reactors or centrifuges and piping between such large equipment can be sampled only using rinse solution samples. Any indirect test method must have been shown to correlate with the condition of the equipment. During validation, the firm should document that testing the uncleaned equipment gives a nonacceptable result for the indirect test.

42.1.5 Establishment of Limits

FDA does not intend to set acceptance specifications or methods for determining whether a cleaning process is validated. It is impractical for FDA to do so due to the wide variation in equipment and products used throughout the bulk and finished dosage form industries. The firm's rationale for the residue limits established should be logical based on the manufacturer's knowledge of the materials involved and be practical, achievable, and verifiable. It is important to define the sensitivity of the analytical methods in order to set reasonable limits. Some limits that have been mentioned by industry representatives in the literature or in presentations include analytical detection levels such as 10 ppm, biological activity levels such as 1/1000 of the normal therapeutic dose, and organoleptic levels such as no visible residue.

Check the manner in which limits are established. Unlike finished pharmaceuticals where the chemical identities of residuals are known (i.e., from actives, inactives, detergents), bulk processes may have partial reactants and unwanted by-products that may never have been chemically identified. In establishing residual limits, it may not be adequate to focus only on the principal reactant since other chemical variations may be more difficult to remove. There are circumstances where TLC screening, in addition to chemical analyses, may be required. In a bulk process, particularly for very potent chemicals such as some steroids, the issue of by-products needs to be considered if equipment is not dedicated. The objective of the inspection is to ensure that the basis for any limits is scientifically justifiable.

42.1.6 Other Issues

42.1.6.1 Placebo Product

In order to evaluate and validate cleaning processes, some manufacturers have processed a placebo batch in the equipment under essentially the same operating parameters used for processing product. A sample of the placebo batch is then tested for residual contamination. However, we have documented several significant issues that need to be addressed when using a placebo product to validate cleaning processes.

One cannot ensure that the contaminant will be uniformly distributed throughout the system. For example, if the discharge valve or chute of a blender is contaminated, the contaminant would probably not be uniformly dispersed in the placebo; it would most likely be concentrated in the initial discharge portion of the batch. Additionally, if the contaminant or residue is of a larger particle size, it may not be uniformly dispersed in the placebo.

Some firms have made the assumption that a residual contaminant would be worn off the equipment surface uniformly; this is also an invalid conclusion. Finally, the analytical power may be greatly reduced by dilution of the contaminate. Because of such problems, rinse and/or swab samples should be used in conjunction with the placebo method.

42.1.6.2 Detergent

If a detergent or soap is used for cleaning, determine and consider the difficulty that may arise when attempting to test for residues. A common problem associated with detergent

use is its composition. Many detergent suppliers will not provide specific composition, which makes it difficult for the user to evaluate residues. As with product residues, it is important and it is expected that the manufacturer evaluate the efficiency of the cleaning process for the removal of residues. However, unlike product residues, it is expected that no (or for ultrasensitive analytical test methods—very low) detergent levels remain after cleaning. Detergents are not part of the manufacturing process and are only added to facilitate cleaning during the cleaning process. Thus, they should be easily removable. Otherwise, a different detergent should be selected.

42.1.6.3 Test until Clean

Examine and evaluate the level of testing and the retest results since testing until clean is a concept utilized by some manufacturers. They test, resample, and retest equipment or systems until an "acceptable" residue level is attained. For the system or equipment with a validated cleaning process, this practice of resampling should not be utilized and is acceptable only in rare cases. Constant retesting and resampling can show that the cleaning process is not validated since these retests actually document the presence of unacceptable residue and contaminants from an ineffective cleaning process.

Bibliography

1. J. Rodehamel, "Cleaning and maintenance," pp. 82–87, University of Wisconsin's *Control Procedures in Drug Production*, Seminar, July 17–22, 1966, W. Blockstein, Ed., Published by the University of Wisconsin, L.O.C.#66-64234.
2. J.A. Constance, "Why some dust control exhaust systems don't work," *Pharm. Eng.*, (January–February), 24–26 (1983).
3. S.W. Harder, "The validation of cleaning procedures," *Pharm. Technol.*, 8(5), 29–34 (1984).
4. W.J. Mead, "Maintenance: Its interrelationship with drug quality," *Pharm. Eng.*, 7(3), 29–33 (1987).
5. J.A. Smith, "A modified swabbing technique for validation of detergent residues in clean-in-place systems," *Pharm. Technol.*, 16(1), 60–66 (1992).
6. G.L. Fourman and M.V. Mullen, "Determining cleaning validation acceptance limits for pharmaceutical manufacturing operations," *Pharm. Technol.*, 17(4), 54–60 (1993).
7. P.Y. McCormick and L.F. Cullen, In *Pharmaceutical Process Validation*, I.R. Berry and R.A. Nash, Eds, 2nd Ed., pp. 319–349, 1993.

CLV-42.2

WHO Good Manufacturing Guidelines for Cleaning Validation

Quality Assurance of Pharmaceuticals—A Compendium of Guidelines and Related Materials—Volume 2 Updated and Revised Edition—Good Manufacturing Practices and Inspection (WHO; 2003; 223 pages): 2. WHO good manufacturing practices: starting materials: Pharmaceutical excipients: 1. General considerations

42.2.1 Cleaning Program

Where multipurpose equipment is in use, it is important to be able to determine previous usage when investigating cross-contamination or the possibility of such contamination. An equipment cleaning and use log, while desirable and perhaps preferable, is not the only method of determining prior use. Any documentation system, which clearly identifies the previous batch and shows that the equipment was cleaned, is acceptable.

For operations where multiple grades of the same chemical entity are processed, there must be documentation showing that the previous grade was removed. Validation data must exist to prove acceptability of the cleaning procedure.

Cleaning of multiple-use equipment should be confirmed. The manufacturer should determine the effectiveness of the cleaning procedure for each excipient or intermediate chemical used in that particular piece of equipment. The validation data required depend on the types of materials being made in the multiple-use equipment and the impact of trace contaminants on drug safety and performance. Validation data should verify that the cleaning process has removed residues to an acceptable level.

As an example, an equipment cleaning program may include, but is not limited to, the following.

42.2.1.1 Detailed Cleaning Procedure

There should be a written equipment cleaning procedure that provides details of what should be done and which cleaning materials should be used. Some manufacturers list the specific solvents used for each excipient and intermediate.

42.2.1.2 Sampling Plan

There should be some periodic testing after cleaning to ensure that the surface has been cleaned to the required level. One common method is to analyze the final rinse water or solvent for the presence of the substance last used in that piece of equipment. In some cases, visual inspections may be appropriate. A specific analytical method to determine residual substances may not always be available, but is preferred. The need for an analytical

method would be based on the potential adverse effect on product quality, performance, or safety. When safety is a concern, there should be a specific analytical determination for a residual substance.

42.2.1.3 Analytical Methods/Cleaning Limits

The toxicity of the residual materials should be considered when deciding on the appropriate analytical method and the residual cleaning limits. The residue limits established for each piece of apparatus should be practical, achievable, and verifiable. The manufacturer should be able to show, with supporting data, that the residual level permitted is scientifically based. Another factor to consider is the possible nonuniformity of the residue. The level of residue found by random sampling, such as taking a swab from a limited area on a piece of equipment, does not necessarily represent the highest level of contamination.

CLV-42.3

Health Products and Food Branch Inspectorate Guidance Document Cleaning Validation Guidelines GUIDE-0028

42.3.1 Scope

Disclaimer

This document does not constitute part of the Food and Drugs Act (Act) or the Food and Drugs Regulations (Regulations) and in the event of any inconsistency or conflict between that Act or Regulations and this document, the Act or the Regulations take precedence. This document is an administrative document that is intended to facilitate compliance by the regulated party with the Act, the Regulations, and the applicable administrative policies. This document is not intended to provide legal advice regarding the interpretation of the Act or Regulations. If a regulated party has questions about their legal obligations or responsibilities under the Act or Regulations, they should seek the advice of legal counsel.

This document on cleaning validation is intended to address special considerations and issues pertaining to validation of cleaning procedures for equipment used in the manufacture of pharmaceutical products, radiopharmaceuticals, and biological drugs. The document is also intended to establish inspection consistency and uniformity with respect to equipment cleaning procedures. Principles incorporated in international guidance have been taken into account in the preparation of this document. The document is intended to cover validation of equipment cleaning for the removal of contaminants associated with previous products, residues of cleaning agents as well as the control of potential microbial contaminants.

42.3.2 Introduction

This document provides some guidance on issues and topics related to cleaning validation. This topic reflects an area in pharmaceutical, biological, and radiopharmaceutical manufacturing that is noted as being important by both the inspectorate and the pharmaceutical industry. This guideline has been prepared to provide guidance to inspectors, evaluators, and industry in reviewing the issues covered. Utilization of this information should facilitate compliance with Division 2 Part C of the *Food and Drugs Regulations*.

It is not intended that the recommendations made in these guidelines become requirements under all circumstances. Information provided in the document for limits to be applied in defined circumstances as well as the number of batches to be utilized for cleaning validation studies is for guidance purposes only. Inspectors, evaluators, and industry may consider other limits if proposed and documented in accordance with appropriate scientific justification.

42.3.3 Principles

3.1 The objective of cleaning validation is to verify the effectiveness of the cleaning procedure for the removal of product residues, degradation products, preservatives, excipients, and/or cleaning agents as well as the control of potential microbial contaminants. In addition, one needs to ensure that there is no risk associated with cross-contamination of active ingredients.

3.2 Cleaning procedures must strictly follow carefully established and validated methods.

3.3 Appropriate cleaning procedures must be developed for all product-contact equipment used in the production process. Consideration should also be given to noncontact parts into which product may migrate (e.g., seals, flanges, mixing shaft, fans of ovens, heating elements, etc.).

3.4 Relevant process equipment cleaning validation methods are required for biological drugs because of their inherent characteristics (proteins are sticky by nature), parenteral product purity requirements, the complexity of equipment, and the broad spectrum of materials that need to be cleaned.

3.5 Cleaning procedures for products and processes that are very similar do not need to be individually validated. This could be dependent on what is common, equipment and surface area, or an environment involving all product-contact equipment.

It is considered acceptable to select a representative range of similar products and processes. The physical similarities of the products, the formulation, the manner and quantity of use by the consumer, the nature of other product previously manufactured, and the size of batch in comparison to previously manufactured product are critical issues that justify a validation program.

A single validation study considering the worst case can then be carried out, which takes account of the relevant criteria.

For biological drugs, including vaccines, bracketing may be considered acceptable for similar products and/or equipment, provided appropriate justification, based on sound and scientific rationale, is given. Some examples are cleaning of fermenters of the same design but with different vessel capacity used for the same type of recombinant proteins expressed in the same rodent cell line and cultivated in closely related growth media and a multiantigen vaccine used to represent the individual antigen or other combinations of them when validating the same or similar equipment that is used at stages of formulation (adsorption) and/or holding. Validation of cleaning of fermenters should be done on an individual pathogen basis.

42.3.4 Validation of Cleaning Processes

4.1 As a general concept, until the validation of the cleaning procedure has been completed, the product-contact equipment should be dedicated.

4.2 In a multiproduct facility, the effort of validating the cleaning of a specific piece of equipment that has been exposed to a product and the cost of permanently dedicating the equipment to a single product should be considered.

4.3 Equipment cleaning validation may be performed concurrently with actual production steps during process development and clinical manufacturing. Validation programs should be continued through full-scale commercial production.

4.4 It is usually not considered acceptable to test-until-clean. This concept involves cleaning, sampling, and testing with repetition of this sequence until an acceptable residue limit is attained.

4.5 Products that simulate the physicochemical properties of the substance to be removed may be considered for use instead of the substances themselves, when such substances are either toxic or hazardous.

4.6 Raw materials sourced from different suppliers may have different physical properties and impurity profiles. When applicable such differences should be considered when designing cleaning procedures, as the materials may behave differently.

4.7 All pertinent parameters should be checked to ensure that the process as it will ultimately be run is validated. Therefore, if critical temperatures are needed to effect cleaning, then these should be verified. Any chemical agents added should be verified for type as well as quantity. Volumes of wash and rinse fluids, and velocity measurements for cleaning fluids should be measured as appropriate.

4.8 If automated procedures are utilized (CIP), consideration should be given to monitoring the critical control points and the parameters with appropriate sensors and alarm points to ensure the process is highly controlled.

4.9 During a campaign (production of several batches of the same product), cleaning between batches may be reduced. The number of lots of the same product that could be manufactured before a complete/full cleaning is done should be determined.

4.10 Validation of cleaning processes should be based on a worst-case scenario, including

i. Challenge of the cleaning process to show that the challenge soil can be recovered in sufficient quantity or demonstrate log removal to ensure that the cleaning process is indeed removing the soil to the required level

ii. The use of reduced cleaning parameters such as overloading of contaminants, overdrying of equipment surfaces, minimal concentration of cleaning agents, and/or minimum contact time of detergents

4.11 At least three (3) consecutive applications of the cleaning procedure should be performed and shown to be successful in order to prove that the method is validated. Equipment that is similar in design and function may be grouped and a worst case established for validation.

42.3.5 Equipment and Personnel

42.3.5.1 Equipment

5.1 All processing equipment should be specifically designed to facilitate cleanability and permit visual inspection and, whenever possible, the equipment should be made of smooth surfaces of nonreactive materials.

5.2 Critical areas (i.e., those hardest to clean) should be identified, particularly in large systems that employ semiautomatic or fully automatic CIP systems.

5.3 Dedicated product-contact equipment should be used for products that are difficult to remove (e.g., tarry or gummy residues in bulk manufacturing), for equipment that is difficult to clean (e.g., bags for fluid bed dryers), or for products with a high safety risk (e.g., biologicals or products of high potency that may be difficult to detect below an acceptable limit).

5.4 In a bulk process, particularly for very potent chemicals such as some steroids, the issue of by-products needs to be considered if equipment is not dedicated.

42.3.5.2 Personnel

5.5 It is difficult to validate a manual cleaning procedure (i.e., an inherently variable/cleaning procedure). Therefore, operators carrying out manual cleaning procedures should be adequately trained, monitored, and periodically assessed.

42.3.6 Microbiological Considerations

6.1 Whether or not CIP systems are used for the cleaning of processing equipment, microbiological aspects of equipment cleaning should be considered. This consists largely of preventive measures rather than removal of contamination once it has occurred.

6.2 There should be some documented evidence that routine cleaning and storage of equipment do not allow microbial proliferation. For example, equipment should be dried before storage, and under no circumstances should stagnant water be allowed to remain in equipment subsequent to cleaning operations. Time frames for the storage of unclean equipment, prior to commencement of cleaning, as well as time frames and conditions for the storage of cleaned equipment should be established.

6.3 The control of the bio-burden through adequate cleaning and storage of equipment is important to ensure that subsequent sterilization or sanitization procedures achieve the necessary assurance of sterility. This is also particularly important from the standpoint of the control of pyrogens in sterile processing since equipment sterilization processes may not be adequate to achieve significant inactivation or removal of pyrogens.

42.3.7 Documentation

7.1 Detailed cleaning procedures are to be documented in SOPs

7.2 A cleaning validation protocol is required to define how the cleaning process will be validated. It should include the following:

- The objective of the validation process
- Responsibilities for performing and approving the validation study
- Description of the equipment to be used
- The interval between the end of production and the beginning of the cleaning procedure
- The number of lots of the same product, which could be manufactured during a campaign before a full cleaning is done
- Detailed cleaning procedures to be used for each product, each manufacturing system, or each piece of equipment
- The number of cleaning cycles to be performed consecutively
- Any routine monitoring requirement
- Sampling procedures, including the rationale for why a certain sampling method is used
- Clearly defined sampling locations
- Data on recovery studies, where appropriate
- Validated analytical methods including the limit of detection and the limit of quantitation of those methods
- The acceptance criteria, including the rationale for setting the specific limits
- Other products, processes, and equipment for which the planned validation is valid according to a "bracketing" concept
- Change control/revalidation

7.3 Depending on the complexity of the system and cleaning processes, the amount of documentation necessary for executing various cleaning steps or procedures may vary.

7.4 When more complex cleaning procedures are required, it is important to document the critical cleaning steps. In this regard, specific documentation on the equipment itself, which includes information about who cleaned it, when the cleaning was carried out, and the product that was previously processed on the equipment being cleaned, should be available. However, for relatively simple cleaning operations, mere documentation that the overall cleaning process was performed might be sufficient.

7.5 Other factors such as history of cleaning, residue levels found after cleaning, and variability of test results may also dictate the amount of documentation required. For example, when variable residue levels are detected following cleaning, particularly for a process that is believed to be acceptable, one must establish the effectiveness of the process and of operator performance. Appropriate evaluations must be made, and when operator performance is deemed a problem, more extensive documentation (guidance) and training may be required.

7.6 A final validation report should be prepared. The conclusions of this report should state whether the cleaning process has been validated successfully. Limitations that apply to the use of the validated method should be defined

(e.g., the analytical limit at which cleanliness can be determined). The report should be approved by management.

42.3.8 Analytical Methods

8.1 The analytical methods used to detect residuals or contaminants should be specific for the substance or the class of substances to be assayed (e.g., product residue, detergent residue, and/or endotoxin) and should be validated before the cleaning validation study is carried out.

8.2 If levels of contamination or residual are not detected, this does not mean that there is no residual contaminant present after cleaning. It only means that levels of contaminant greater than the sensitivity or detection limit of the analytical method are not present in the sample.

8.3 In the case of biological drugs, the use of product-specific assay(s) such as immunoassay(s) to monitor the presence of biological carryover may not be adequate; a negative test may be the result of denaturation of protein epitope(s). Product-specific assay(s) can be used in addition to TOC for the detection of protein residue.

8.4 The analytical method and the percent recovery of contaminants should be challenged in combination with the sampling method(s) used (see below). This is to show that contaminants can be recovered from the equipment surface and to show the level of recovery as well as the consistency of recovery. This is necessary before any conclusions can be made based on the sample results. A negative test may also be the result of poor sampling technique.

42.3.9 Sampling, Rinsing, Rinse Samples, and Detergents

42.3.9.1 Sampling

9.1 There are two general types of sampling that are considered to be acceptable: direct surface sampling (swab method) and indirect sampling (use of rinse solutions). A combination of the two methods is generally the most desirable, particularly in circumstances where accessibility of equipment parts can mitigate against direct surface sampling.

9.2 Direct surface sampling

i. Areas that are hardest to clean and that are reasonably accessible can be evaluated by the direct sampling method, leading to establishing a level of contamination or residue per given surface area.

   Additionally, residues that are "dried out" or are insoluble can be sampled by physical removal.

ii. The suitability of the material to be used for sampling and of the sampling medium should be determined. The ability to recover a sample accurately may

be affected by the choice of sampling material. It is important to ensure that the sampling medium and solvent (used for extraction from the medium) are satisfactory and can be readily used.

9.3 Rinse samples

i. Rinse samples allow the sampling of a large surface area and of inaccessible systems or ones that cannot be routinely disassembled. However, consideration should be given to the fact that the residue or contaminant may be insoluble or may be physically occluded in the equipment.

ii. A direct measurement of the residue or contaminant in the relevant solvent should be made when rinse samples are used to validate the cleaning process.

9.4 Indirect testing such as conductivity and TOC testing may be of some value for routine monitoring once a cleaning process has been validated. This would be true where reactors or centrifuges and piping between such large equipment can be sampled only using rinse solution samples.

9.5 If the placebo method is used to validate the cleaning process, then it should be used in conjunction with rinse and/or swab samples. It is difficult to provide assurance that the contaminate will be uniformly dispersed throughout the system or that it would be worn off the equipment surface uniformly. Additionally, if the contaminant or residue is of large enough particle size, it may not be uniformly dispersed in the placebo. Finally, the analytical power of the assay may be greatly reduced by dilution of the contaminant.

9.6 It is important to use visual inspection in addition to analytical methodology to ensure that the process is acceptable.

42.3.9.2 Detergents

9.7 When detergents are used in the cleaning process, their composition should be known to the user and their removal should be demonstrated. The manufacturer should ensure that they are notified by the detergent supplier of any changes in the formulation of the detergent.

9.8 Detergents should be easily removable, being used to facilitate the cleaning during the cleaning process. Acceptable limits should be defined for detergent residues after cleaning. The possibility of detergent breakdown should also be considered when validating cleaning procedures.

42.3.9.3 Last Rinse

9.9 Water for injection should be used as the last rinse for product-contact equipment to be utilized in the fabrication of sterile products.

9.10 Purified water is considered acceptable as the last rinse for product-contact equipment used in the fabrication of nonsterile products or sterile products for ophthalmic use.

Note: Because of the presence of varying levels of organic and inorganic residues as well as chlorine, tap water should not be used in the last rinse of any cleaning procedure for product-contact equipment.

42.3.10 Establishment of Limits

10.1 The fabricator's rationale for selecting limits for product residues should be logical and based on the materials involved and their therapeutic dose. The limits should be practical, achievable, and verifiable.

10.2 In establishing product residual limits, it may not be adequate to focus only on the main reactant since by-products/chemical variations (active decomposition material) may be more difficult to remove. In addition to chemical testing, TLC screening may be needed in certain circumstances.

10.3 The approach for setting limits can be

1. Product-specific cleaning validation for all products
2. Grouping into product families and choosing a worst-case product
3. Grouping by properties (e.g., solubility, potency, toxicity, or formulation ingredients known to be difficult to clean)
4. Setting limits on not allowing more than a certain fraction of carryover
5. Different safety factors for different dosage forms

10.4 Carryover of product residues should meet defined criteria, for example the most stringent of the following criteria (i, ii, iii):

i. NMT 0.1% of the normal therapeutic dose of any product to appear in the maximum daily dose of the following product.

ii. NMT 10 ppm of any product to appear in another product.

iii. No quantity of residue to be visible on the equipment after cleaning procedures are performed. Spiking studies should determine the concentration at which the most active ingredients are visible.

iv. For certain highly sensitizing or highly potent ingredients (such as penicillins, cephalosporins, or potent steroids and cytotoxics), the limits should be below the limit of detection by the best available analytical methods. In practice, this may mean that dedicated plants are used for these products.

42.3.11 Change Control/Revalidation

11.1 A change control system is in place to ensure that all changes that might impact the cleaning process are assessed and documented. Significant changes should follow satisfactory review and authorization of the documented change proposal through the change control procedure. Minor changes or changes having no direct impact on final or in-process product quality should be handled through the documentation system.

The review should include consideration of revalidation of the cleaning procedure.

11.2 Changes that require evaluation and likely revalidation include but are not limited to

- Changes in the cleaning procedure.
- Changes in the raw material sources.

- Changes in the formulation and/or process of products.
- New products.
- Changes in the formulation of detergents.
- New detergents.
- Modifications of equipment.

11.3 The cleaning process should be reassessed at defined intervals and revalidated as necessary. Manual methods should be reassessed at more frequent intervals than CIP systems.

Bibliography

1. FDA, Guide to Inspections of Validation of Cleaning Processes, 1993.
2. Pharmaceutical Inspection Convention, Recommendations on Validation Master Plan, Installation and Operational Qualification, Non-Sterile Process Validation and Cleaning Validation, 2004.

CLV-42.4

Qualification and Validation

EUROPEAN COMMISSION
ENTERPRISE DIRECTORATE-GENERAL

Single market, regulatory environment, industries under vertical legislation
Pharmaceuticals and cosmetics

Brussels, July 2001

Working Party on Control of Medicines and Inspections

Final Version of **Annex 15** to the EU Guide to Good Manufacturing Practice

Title: **Qualification and validation**

First discussion in drafting group	
Discussion at the working Party on Control of Medicines and Inspection for release for consultation	16 September 1999
Pharmaceutical Committee	28 September 1999
Released for consultation	30 October 1999
Deadline for comments	28 February 2000
Final approval by Inspector's working party	December 2000
Pharmaceutical Committee (for information)	April 2001
Date for coming into operation	September 2001

Note that this document is based in the PICS/S recommendations

Table of Contents

3

QUALIFICATION AND VALIDATION

Principle

1. This Annex describes the principles of qualification and validation which are applicable to the manufacture of medicinal products. It is a requirement of GMP that manufacturers identify what validation work is needed to prove control of the critical aspects of their particular operations. Significant changes to the facilities, the equipment and the processes, which may affect the quality of the product, should be validated. A risk assessment approach should be used to determine the scope and extent of validation.

4

PLANNING FOR VALIDATION

2. All validation activities should be planned. The key elements of a validation programme should be clearly defined and documented in a validation master plan (VMP) or equivalent documents.

3. The VMP should be a summary document which is brief, concise and clear.

4. The VMP should contain data on at least the following:
(a) validation policy;
(b) organisational structure of validation activities;
(c) summary of facilities, systems, equipment and processes to be validated;
(d) documentation format: the format to be used for protocols and reports;
(e) planning and scheduling;
(f) change control;
(g) reference to existing documents.

5. In case of large projects, it may be necessary to create separate validation master plans.

DOCUMENTATION

6. A written protocol should be established that specifies how qualification and validation will be conducted. The protocol should be reviewed and approved. The protocol should specify critical steps and acceptance criteria.

7. A report that cross-references the qualification and/or validation protocol should be prepared, summarising the results obtained, commenting on any deviations observed, and drawing the necessary conclusions, including recommending changes necessary to correct deficiencies. Any changes to the plan as defined in the protocol should be documented with appropriate justification.

8. After completion of a satisfactory qualification, a formal release for the next step in qualification and validation should be made as a written authorisation.

5

QUALIFICATION

Design qualification

9. The first element of the validation of new facilities, systems or equipment could be design qualification (DQ).

10. The compliance of the design with GMP should be demonstrated and documented.

Installation qualification

11. Installation qualification (IQ) should be performed on new or modified facilities, systems and equipment.

12. IQ should include, but not be limited to the following:
(a) installation of equipment, piping, services and instrumentation checked to current engineering drawings and specifications;
(b) collection and collation of supplier operating and working instructions and maintenance requirements;
(c) calibration requirements;
(d) verification of materials of construction.

Operational qualification

13. Operational qualification (OQ) should follow Installation qualification.

14. OQ should include, but not be limited to the following:
(a) tests that have been developed from knowledge of processes, systems and equipment;
(b) tests to include a condition or a set of conditions encompassing upper and lower operating limits, sometimes referred to as “worst case” conditions.

15. The completion of a successful Operational qualification should allow the finalisation of calibration, operating and cleaning procedures, operator training and preventative maintenance requirements. It should permit a formal "release" of the facilities, systems and equipment.

Performance qualification

16. Performance qualification (PQ) should follow successful completion of Installation qualification and Operational qualification.

17. PQ should include, but not be limited to the following:
(a) tests, using production materials, qualified substitutes or simulated product, that have been developed from knowledge of the process and the facilities, systems or equipment;

(b) tests to include a condition or set of conditions encompassing upper and lower operating limits.

18. Although PQ is described as a separate activity, it may in some cases be appropriate to perform it in conjunction with OQ.

Qualification of established (in-use) facilities, systems and equipment

19. Evidence should be available to support and verify the operating parameters and limits for the critical variables of the operating equipment. Additionally, the calibration, cleaning, preventative maintenance, operating procedures and operator training procedures and records should be documented.

PROCESS VALIDATION

General

20. The requirements and principles outlined in this chapter are applicable to the manufacture of pharmaceutical dosage forms. They cover the initial validation of new processes, subsequent validation of modified processes and re-validation.

21. Process validation should normally be completed prior to the distribution and sale of the medicinal product (prospective validation). In exceptional circumstances, where this is not possible, it may be necessary to validate processes during routine production (concurrent validation). Processes in use for some time should also be validated (retrospective validation).

22. Facilities, systems and equipment to be used should have been qualified and analytical testing methods should be validated. Staff taking part in the validation work should have been appropriately trained.

23. Facilities, systems, equipment and processes should be periodically evaluated to verify that they are still operating in a valid manner.

Prospective validation

24. Prospective validation should include, but not be limited to the following:
(a) short description of the process;
(b) summary of the critical processing steps to be investigated;
(c) list of the equipment/facilities to be used (including measuring/monitoring/recording equipment) together with its calibration status
(d) finished product specifications for release;
(e) list of analytical methods, as appropriate;
(f) proposed in-process controls with acceptance criteria;
(g) additional testing to be carried out, with acceptance criteria and analytical validation, as appropriate;
(h) sampling plan;

(i) methods for recording and evaluating results
(j) functions and responsibilities;
(k) proposed timetable.

25. Using this defined process (including specified components) a series of batches of the final product may be produced under routine conditions. In theory the number of process runs carried out and observations made should be sufficient to allow the normal extent of variation and trends to be established and to provide sufficient data for evaluation. It is generally considered acceptable that three consecutive batches/runs within the finally agreed parameters, would constitute a validation of the process.

26. Batches made for process validation should be the same size as the intended industrial scale batches.

27. If it is intended that validation batches be sold or supplied, the conditions under which they are produced should comply fully with the requirements of Good Manufacturing Practice, including the satisfactory outcome of the validation exercise, and with the marketing authorisation.

Concurrent validation

28. In exceptional circumstances it may be acceptable not to complete a validation programme before routine production starts.

29. The decision to carry out concurrent validation must be justified, documented and approved by authorised personnel.

30. Documentation requirements for concurrent validation are the same as specified for prospective validation.

Retrospective validation

31. Retrospective validation is only acceptable for well-established processes and will be inappropriate where there have been recent changes in the composition of the product, operating procedures or equipment.

32. Validation of such processes should be based on historical data. The steps involved require the preparation of a specific protocol and the reporting of the results of the data review, leading to a conclusion and a recommendation.

33. The source of data for this validation should include, but not be limited to batch processing and packaging records, process control charts, maintenance

log books, records of personnel changes, process capability studies, finished product data, including trend cards and storage stability results.

34. Batches selected for retrospective validation should be representative of all batches made during the review period, including any batches that failed to meet specifications, and should be sufficient in number to demonstrate process consistency. Additional testing of retained samples may be needed to obtain the necessary amount or type of data to retrospectively validate the process.

35. For retrospective validation, generally data from ten to thirty consecutive batches should be examined to assess process consistency, but fewer batches may be examined if justified.

CLEANING VALIDATION

36. Cleaning validation should be performed in order to confirm the effectiveness of a cleaning procedure. The rationale for selecting limits of carry over of product residues, cleaning agents and microbial contamination should be logically based on the materials involved. The limits should be achievable and verifiable.

37. Validated analytical methods having sensitivity to detect residues or contaminants should be used. The detection limit for each analytical method should be sufficiently sensitive to detect the established acceptable level of the residue or contaminant.

38. Normally only cleaning procedures for product contact surfaces of the equipment need to be validated. Consideration should be given to non-contact parts. The intervals between use and cleaning as well as cleaning and reuse should be validated. Cleaning intervals and methods should be determined.

39. For cleaning procedures for products and processes which are similar, it is considered acceptable to select a representative range of similar products and processes. A single validation study utilising a “worst case” approach can be carried out which takes account of the critical issues.

40. Typically three consecutive applications of the cleaning procedure should be performed and shown to be successful in order to prove that the method is validated.

41. "Test until clean". is not considered an appropriate alternative to cleaning validation.

42. Products which simulate the physicochemical properties of the substances to be removed may exceptionally be used instead of the substances themselves, where such substances are either toxic or hazardous.

CHANGE CONTROL

43. Written procedures should be in place to describe the actions to be taken if a change is proposed to a starting material, product component, process equipment, process environment (or site), method of production or testing or any other change that may affect product quality or reproducibility of the process. Change control procedures should ensure that sufficient supporting data are generated to demonstrate that the revised process will result in a product of the desired quality, consistent with the approved specifications.

44. All changes that may affect product quality or reproducibility of the process should be formally requested, documented and accepted. The likely impact of the change of facilities, systems and equipment on the product should be evaluated, including risk analysis. The need for, and the extent of, re-qualification and re-validation should be determined.

REVALIDATION

45. Facilities, systems, equipment and processes, including cleaning, should be periodically evaluated to confirm that they remain valid. Where no significant changes have been made to the validated status, a review with evidence that facilities, systems, equipment and processes meet the prescribed requirements fulfils the need for revalidation.

10

GLOSSARY

Definitions of terms relating to qualification and validation which are not given in the glossary of the current EC Guide to GMP, but which are used in this Annex, are given below.

Change Control

A formal system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect the validated status of facilities, systems, equipment or processes. The intent is to determine the need for action that would ensure and document that the system is maintained in a validated state.

Cleaning Validation

Cleaning validation is documented evidence that an approved cleaning procedure will provide equipment which is suitable for processing medicinal products.

Concurrent Validation

Validation carried out during routine production of products intended for sale.

Design qualification (DQ)

The documented verification that the proposed design of the facilities, systems and equipment is suitable for the intended purpose.

Installation Qualification (IQ)

The documented verification that the facilities, systems and equipment, as installed or modified, comply with the approved design and the manufacturer's recommendations.

Operational Qualification (OQ)

The documented verification that the facilities, systems and equipment, as installed or modified, perform as intended throughout the anticipated operating ranges.

Performance Qualification (PQ)

The documented verification that the facilities, systems and equipment, as connected together, can perform effectively and reproducibly, based on the approved process method and product specification.

Process Validation

The documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes.

11

Prospective Validation

Validation carried out before routine production of products intended for sale.

Retrospective Validation

Validation of a process for a product which has been marketed based upon accumulated manufacturing, testing and control batch data.

Re-Validation

A repeat of the process validation to provide an assurance that changes in the process/equipment introduced in accordance with change control procedures do not adversely affect process characteristics and product quality.

Risk analysis
Method to assess and characterise the critical parameters in the functionality of an equipment or process.
.

Simulated Product

A material that closely approximates the physical and, where practical, the chemical characteristics (e.g. viscosity, particle size, pH etc.) of the product under validation. In many cases, these characteristics may be satisfied by a placebo product batch.

System

A group of equipment with a common purpose.

Worst Case

A condition or set of conditions encompassing upper and lower processing limits and circumstances, within standard operating procedures, which pose the greatest chance of product or process failure when compared to ideal conditions. Such conditions do not necessarily induce product or process failure.

CLV-43

Sampling Tools

43.1 Remote Swabbing and Microbiological Sampling Tools

Sampling is the act of capturing product or specimen from a process for the purpose of analysis.

Samples are generally taken for the following reasons:

a. To ensure that a particular process is working according to specifications
b. As part of troubleshooting in determining the source of product contamination

When sampling from pharmaceutical equipment is done, it is essential that the sample is taken without contaminating the product and also that a representative sample is collected so that a true picture of the process can be depicted by the results.

Like all other manufacturing process samples, cleaning validation samples also play a significant role in maintaining the quality and efficacy of finished products. While taking representative samples from a production equipment or system, care must be taken to use appropriate samplers, specifically designed for the purpose. In the following sections, details of such samplers and accessories are given for the use of validation professionals.

43.2 Remote Swabbing and Microbiological Sampling Tools

These tools are made of anodized aluminum (for lightweight), standard tool extendible up to 10 ft with optional extensions to 25 ft, to take swab or microbiological samples from distant locations such as surfaces of large mixers, blenders, dryers, reactors, and so on, without someone actually getting inside the equipment. At the tip of this tool there is an anodized aluminum adjustable angle adapter, which can be bent up to 90° in order to gain access to the location to be swabbed. Five different types of clips may be attached to the tip of the adjustable angle adapter in order to hold a swab (with or without a handle), a wipe, a microbiological sampling plate (agar plate), or a swab from a microbiological sampling tube (Swube). This tool can be completely dismantled and reassembled in a few minutes, and is sterilizable. The plastic collars inside the tool segments can be sanitized with alcohol.

FIGURE 43.1
Remote swabbing and microbiological sampling tool.

An optional mirror attachment with plastic mirror sizes of $3'' \times 3''$ and $6'' \times 6''$ and a flashlight attachment are also available (Figures 43.1 and 43.2).

43.3 Teflon Template Tool

This tool is just like the tool described above, except that a Teflon template holder with a Teflon template having an opening of desired dimensions is attached to it, and is used in conjunction with the swabbing tool for swabbing a predetermined surface area. Teflon templates are available with custom-made sizes, shapes, and surface areas (Figure 43.3).

43.4 Accessories

Suction cups: These are used in conjunction with the swabbing tool for microbiological sampling with agar plates. They are 2″ in diameter and individually packaged; two different types are available (Figure 43.4):

a. Made of poly vinyl chloride (PVC), cannot be steam sterilized, may be sanitized with alcohol, and disposable
b. Made of silicone, can be steam sterilized, and reusable

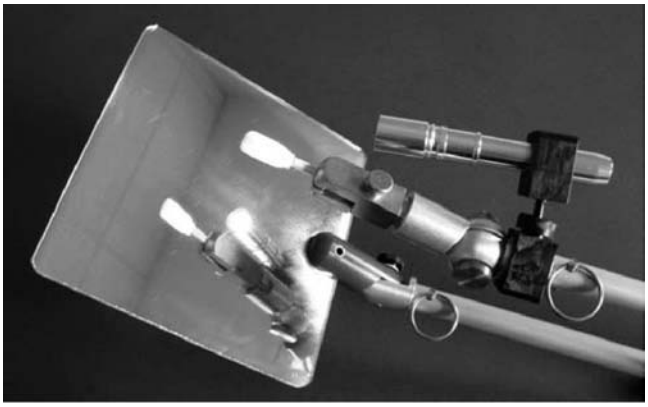


FIGURE 43.2
Remote swabbing tool with optional mirror and flashlight attachment.

FIGURE 43.3
Teflon template swabbing tool.

Clips: Five different types of clips are available:

a. Made of 316 stainless steel and electropolished for microbiological sampling using agar plates. Steam, dry heat, ethylene oxide (ETO), and gamma radiation sterilizable.
b. Made of 316 stainless steel and electropolished for swab sampling using swabs with or without handles, filter paper, or wipes. Especially suitable for Texwipe alpha swabs TX761 and TX714A (available from VWR Scientific). Steam, dry heat, ETO, and gamma radiation sterilizable.
c. Made of an FDA-approved white plastic, for the same application as described in (b) above. May be sanitized with alcohol, but not sterilizable. Designed to avoid scratching the surface being swabbed.
d. Made of an FDA-approved amber-colored special plastic for microbiological sampling using swabs from microbiological tubes (Swubes). Steam, dry heat, ETO, and gamma radiation sterilizable.
e. Made of 316 stainless steel for microbiological sampling using culture swabs from DIFCO Laboratories (Figures 43.5 and 43.6).

Adjustable angle adapter: Made of anodized aluminum; this part accepts all the clips described above. The angle can be adjusted to 90° (Figure 43.7).

Teflon template holder: Made of 316 stainless steel; used with the Teflon template tool to hold the template (Figure 43.8).

Teflon template: Made of Teflon, 6″ × 6″ external dimensions, with an opening of desired dimensions.

Aluminum clutches and plastic collars: Aluminum clutches to provide grip between the segments of the tool (Figure 43.9).

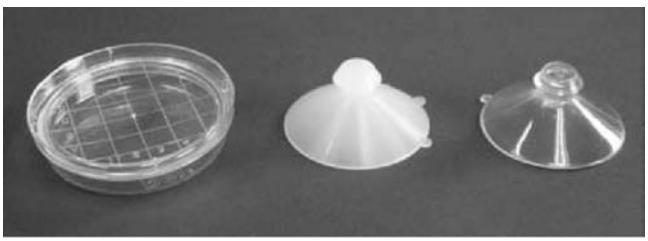


FIGURE 43.4
Suction cups.

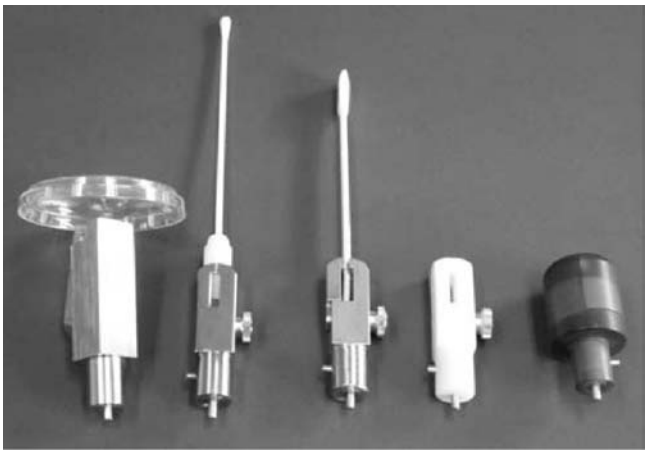


FIGURE 43.5
Clips for use with Rodak plates, Texwipe swabs, wipes, and Swubes.

Clip 4A

Use with agar plates
and suction cups

Clip 4B

For use with tex wipe
alpha swabs and wipes

Clip 4C

Clip 4D

Clip 4E

FIGURE 43.6
Clip 4A: For use with agar plates and suction cups. Clip 4B: For use with Texwipe alpha swabs and wipes. Clip 4C: Delrin model of Clip 4B. Clip 4D: For use with Swubes. Clip 4E: For use with culture swabs.

FIGURE 43.7
Adjustable angle adapter.

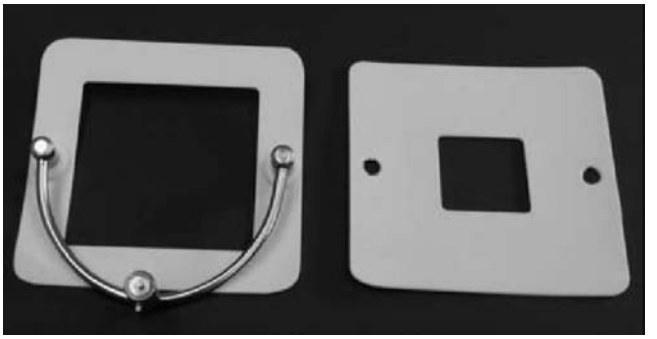


FIGURE 43.8
Teflon template holder with a 4″ × 4″ Teflon template.

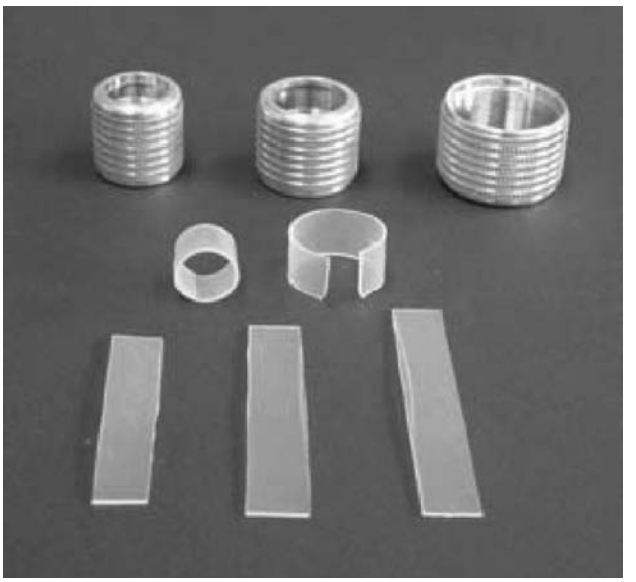


FIGURE 43.9
Plastic collars and aluminum clutches for the cleaning validation kit.

FIGURE 43.10
Mirror attachment.

Mirrors: To be able to see underneath a surface while swabbing or inspecting. 3″ × 3″ and 6″ × 6″ sizes are available.

Flashlight: To be able to illuminate the surface being swabbed; lightweight, LED.

Mirror and flashlight attachments: The mirror attachment assembly includes the mirror with adapter, a plastic collar, and an 8″-long aluminum tube. The flashlight attachment assembly includes the flashlight and the plastic collar (Figures 43.10 and 43.11).

Ball spring pin: To lock the adapters onto the tool.

Hand grip: To prevent the tool from slipping from the hand.

End cap: To cap the open end of the tool, plastic, black or white.

43.5 Cleaning Validation Coupons

Cleaning validation coupons are used in the laboratory to validate a proposed swabbing method before using that method on the actual surface, which is the subject of cleaning

FIGURE 43.11
Flashlight.

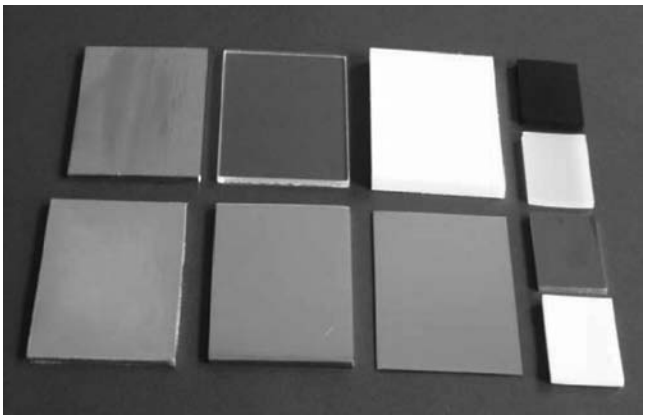


FIGURE 43.12
Cleaning validation coupons in various materials.

validation. For example, if your proposed method for swabbing involves a solvent, say methanol, how do you know if that solvent and the swabbing technique you are going to use will actually recover the residue from the surface? In order to determine the efficiency of your swabbing method in recovering the residue, a cleaning validation coupon, matching the material of construction and the finish of the subject surface, is spiked with a known amount of a solution of the residue of known concentration, dried, and swabbed with your proposed swabbing method and the swab is analyzed for the residue. If the recovery of the residue is within acceptable limits, then you can proceed to do the swabbing on the subject surface (Figure 43.12).

Acknowledgment

Courtesy of GlobePharma (P.O. Box 10837, New Brunswick, NJ 08906-9998, Tel: 732-819-0381; Fax: 732-777-5129) for providing them with pictures, names, and details of the sampling tools used for cleaning validation (www.globepharma.com).

CLV-44

Recommended Readings

Cleaning Validation: A Practical Approach
by Gil Bismuth (Author) and Shosh Neumann (Author)
Publisher: Interpharm/CRC, 2000

This book describes in detail type of contamination and its control, regulatory requirements of cleaning validation, and basic concept. It explains in detail how one can develop a cleaning validation program including a worst-case product matrix, sampling techniques, and analytical methods selection.

Cleaning and Cleaning Validation: A Biotechnology Perspective
by Jon Voss (Author)
Publisher: Interpharm/CRC, 1996

In this book, the author emphasizes more on the design of manufacturing equipment and design challenges related to cleanability of the equipment. The book exclusively describes the cleaning program sequence for vessels, piping, and membrane systems used in biotechnology plants.

The Aqueous Cleaning Handbook: A Guide to Critical-Cleaning Procedures, Techniques and Validation
by Malcolm C. McLaughlin (Author) and Alan S. Zisman (Author)
Publisher: AI Technical Communications, 2005

In this book, valuable information about the history of aqueous cleaners is presented. The book further details how to make best use of aqueous cleaners in cleaning products and components in industrial applications, including pharmaceutical, electronics, metalworking, precision manufacturing, food-and-beverage, and chemical processing.

How to Deal with Cleaning and Contract Manufacturers (Excerpts of Speech Given by Ann Johnson, Senior Cleaning Validation Specialist, Diosynth RTP) (Brief Article). An Article from: *Validation Times (Newsletter),* January 1, 2002; Volume 4, Issue 1
Publisher: Washington Information Source, 2002

Cumberland Swan Repeat Cleaning Validation Problem to be Fixed by End of Year (Human Drugs). An Article from: *Validation Times (Newsletter),* August 1, 2002; Volume 4, Issue 8, Page 7
by Wallace Witkowski (Author)
Publisher: Washington Information Source, 2002

Pharmaceutical Process Validation: An International Third Edition (Drugs and the Pharmaceutical Sciences)
by Robert A. Nash (Editor) and Alfred H. Wachter (Editor)
Publisher: Marcel Dekker, Inc, 2003

Validated Cleaning Technologies for Pharmaceutical Manufacturing
by Destin A. LeBlanc (Author)
Publisher: Interpharm/CRC, 2000

A book for validation professionals who need to design cleaning processes and then validate them. This book discusses how each piece of the cleaning process fits into the validation program, making it more defensible in both internal quality audits and external regulatory audits. The book includes discussion and examples of cleaning systems and regulatory requirements, and also explains how to build a comprehensive cleaning validation program.

Cleaning Validation for the Biotechnology and Biological Industries
by David W. Vincent (Author)
Pharmaceutical Canada, September–October 2008; Volume 9, Number 2

Index

Biotechnology

Cleaning Validation Manual

A Comprehensive Guide for the Pharmaceutical and Biotechnology Industries

During the past decades, enormous progress and enhancement of pharmaceutical manufacturing equipment and its uses have been made. And while there are support documents, books, articles, and online resources available on the principles of cleaning and associated processing techniques, none of them provides a single database with convenient, ready-to-use training tools. Until now. **Cleaning Validation Manual: A Comprehensive Guide for the Pharmaceutical and Biotechnology Industries** elucidates how to train the manpower involved in developing, manufacturing, auditing, and validating of biopharmaceuticals on a pilot scale, leading to scale-up production.

With over 20 easy-to-use template protocols for cleaning validation of extensively used equipment, this book provides technical solutions to assist in fulfilling the training needs of finished product pharmaceutical manufacturers. Drawing on the authors' more than two decades of experience in the pharmaceutical and biotech industries, the text offers hands-on training based on current approaches and techniques. The book does not merely provide guidelines or thought processes; rather, it gives ready-to-use formulas to develop Master Plans, SOPs, and validation protocols. It includes cleaning procedures for the most commonly used equipment in various manufacturing areas and their sampling points, using a pharmaceutical manufacturing site with both sterile and non-sterile operations as the case facility. It also provides the training guidelines on a CD-ROM to enable users to amend or adopt them as necessary.

Grounded in practicality, the book's applicability and accessibility set it apart. It can be used as a guide for implementing a cleaning validation program on site without the help of external consultants, making it a resource that will not be found collecting dust on a shelf, but rather, referred to again and again.

K11299

CRC Press
Taylor & Francis Group
an informa business
www.crcpress.com

6000 Broken Sound Parkway, NW
Suite 300, Boca Raton, FL 33487
270 Madison Avenue
New York, NY 10016
2 Park Square, Milton Park
Abingdon, Oxon OX14 4RN, UK

ISBN: 978-1-4398-2660-7
90000
9 781439 826607

www.crcpress.com

Hai
As

A Comprehensive Guide for the Pharmaceutical and Biotechnology Industries