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Points to Consider for Cleaning Validation

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Preface

This document provides guidance relative to the validation of cleaning for a broad range of processing systems and product types within the pharmaceutical industry. This effort commenced in 1991 in conjunction with individuals representing the biotechnology community. Early on it was agreed to separate the development of cleaning validation guidance into "biotechnology" and "pharmaceutical" segments. The committees worked in parallel for a number of years and shared early drafts to ensure that what would be produced by each committee would be compatible. The biotech effort culminated in PDA's 1995 publication of "Cleaning and Cleaning Validation: A Biotechnology Perspective". The "pharmaceutical" committee continued the development of its document after the publication of the biotech effort, and completed its stand alone guidance in the fall of 1997.

Our goal had always been to outline cleaning validation practices across a range of equipment, process, and product applications and the inclusion of this flexibility was certainly a factor in the length of time it took to complete this effort. During the course of assembling this document, we recognized the commonality of certain themes, issues, and concerns relative to cleaning and cleaning validation across the industry. We also realized that in order to apply the principles in different operating settings, that some narrowing of the document would be necessary. As a result, we have included perspectives on the application of the guidance in various areas: finished pharmaceuticals, bulk pharmaceutical chemicals, biopharmaceuticals and clinical products. Inclusion of biopharmaceuticals in this effort is not intended to replace the more comprehensive coverage provided by our partner committee, but rather to provide greater insight regarding the broad application of the guidance provided herein.

This Technical Report was disseminated in draft for public review and comment prior to publication. Many of the submitted comments have been included in the final document. We believe this approach accomplished the widest possible review of the document and ensures its suitability as a valuable guide to industry in the area of cleaning validation. This document should be considered as a guide; it is not intended to establish any mandatory or implied standard.

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1. Introduction

1.1 Background

In recent years, cleaning has achieved a position of increasing importance in the pharmaceutical industry. The current good manufacturing practices (CGMP) regulations recognize that cleaning is a critical issue to ensure product quality. Virtually every aspect of manufacturing involves cleaning, from the initial stages of bulk production to the final dosage form.

The CGMPs in the United States, Europe and other parts of the world have provided the pharmaceutical industry with general guidance for cleaning requirements. For example, in the U.S., section 211.67 of part 21 of the Code of Federal Regulations (CFR) states that "Equipment and utensils shall be cleaned, maintained, and sanitized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements." Section 211.182 of part 21 of the CFR identifies that cleaning procedures must be documented appropriately, and that a cleaning and use log should be established. In addition to CGMPs, various inspectional guideline documents published by the FDA contain expectations regarding cleaning in the pharmaceutical industry. Cleaning is also addressed in the PIC recommendations on cleaning validation and in the SFSTP Commission report "Validation des procédés de nettoyage."

It has always been the responsibility of the regulated industry and the regulatory agencies to interpret the CGMPs and to create programs and policies which establish the general requirements as specific practices. Recognizing the importance of the relationship between cleaning and product quality, regulatory agencies are demanding greater evidence of cleaning effectiveness through validation or verification.

1.2 Purpose

The purpose of this publication is to identify and discuss the many factors involved in the design, validation, implementation and control of cleaning programs for the pharmaceutical industry.

The document does not attempt to interpret CGMPs but provides guidance for establishing a cleaning validation program. It identifies the many factors to be considered for all segments of the pharmaceutical industry. It also identifies specific points to be considered by dosage form manufacturers, manufacturers of clinical trial materials (CTMs) and manufacturers of bulk pharmaceutical chemicals and biochemicals. The report covers the different approaches which may be appropriate for the different stages of product development from the early research stages to the commercially marketed product.

1.3 Scope

This paper applies to biopharmaceutical, bulk pharmaceutical and finished dosage form operations; liquid, dry, solid and semi-solid dosage forms are covered in both sterile and non-sterile presentations. Both clinical and marketed product cleaning validation programs are identified.

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The manufacture of modern pharmaceuticals is a complex process involving highly technical personnel, complex equipment, sophisticated facilities and complicated processes. Individuals responsible for all aspects of the production, approval and validation of products, such as quality control, quality assurance, engineering, validation, production, research and development, contractors and vendors and regulatory affairs personnel may use this document as a resource for establishing or reviewing the cleaning programs within their facilities.

The validation programs described herein assume that an overall validation program with appropriate controls is already in place for the facility, utilities, equipment and processes. The cleaning of the environment is not specifically covered, however many of the same concerns that are considered for the cleaning of process equipment also impact the cleaning of the environment. The monitoring of microbiological and endotoxin contamination and steps for their elimination are mentioned in several sections and should be part of the cleaning validation program. However this document is not intended to be a comprehensive treatise on microbiological control, or endotoxin limitation. Other documents have addressed microbiological programs and methods for the environmental monitoring which can be applied to cleaning.

1.4 Report Organization

Each of the major topics of this document starts with a general section which applies to all segments of the pharmaceutical industry. Points to be considered for specific industry segments such as biopharmaceuticals, bulk pharmaceutical chemicals, clinical products may vary, depending on the specific product type. A glossary is provided at the end of the report.

Finished Pharmaceuticals
Finished pharmaceuticals represent solid formulations, semi-solid formulations, liquid and aerosol formulations with various routes of administration. Over-the-counter and prescription pharmaceuticals for both human and veterinary use are included in this category.

The common characteristics shared by finished pharmaceuticals are their manufacture by combining raw materials and active ingredients to create the final dosage form.

Pharmaceutical manufacturers often make a large number of product types in one facility; often there are several different strengths prepared of the same product. The cleaning problems include the large number of processes and product types manufactured within one facility. The number of cleaning methods, assays and types of equipment to be tested are often staggering. This is complicated by the issues surrounding the use of non-dedicated equipment. Thus, the establishment of a cleaning validation policy which is applicable to all products is often very difficult.

Biopharmaceuticals
Bioprocess manufacturing, starting with microbial, animal or insect cells, or DNA derived host cells or other cells modified to make a specialized product, can be performed in several ways. Indeed, new methods for bioprocessing are constantly being developed. The most common method is through large scale fermentation (such as bacterial cell culture or mammalian cell culture) followed by highly specific purification steps. Other methods include the development of an antibody in host animals (such as ascites), cloning of cells or tissues, or transgenic generation of cellular components, namely,

proteins. Many in the biopharmaceutical industry consider the stages of fermentation to be similar to other pharmaceutical industry processes. For example, the initial stages of the large scale fermentation have a striking similarity to bulk pharmaceutical chemical production. Later, harvest and purification steps find more in common with pharmaceutical processes. It is important to remember however, that other bioprocessing methods used in the biopharmaceutical industry differ greatly from traditional pharmaceutical processes.

Cleaning for biopharmaceuticals presents special concerns due to the large number of impurities such as cellular debris, waste products of cellular metabolism, media constituents and buffer salts generated or added during manufacture which must be eliminated from the equipment. In the case of mammalian cell cultures, due to the nature of the source material, microbial contamination is of great concern. Identification of the residues is often quite difficult because they may vary from batch to batch. The large variety of proteinaceous materials present in the residue make differentiation of the contaminants from one another a challenge.

Due to the nature of the biopharmaceutical production, multi-product facilities represent an area of regulatory concern. In order to control the production within a multi-product facility, it is necessary to ensure that special precautions are taken which preclude product to product carryover. Cleaning is an integral part of the strategies designed to ensure that there is no cross-contamination in these facilities. The terms cleaning and cleaning validation in multi-product facilities often include the facility itself, and therefore emphasis is placed on changeover validation.

Cleaning for biotechnology products has been described in "Cleaning and Cleaning Validation: A Biotechnology Perspective," PDA, Bethesda, MD, 1996.

Bulk Pharmaceutical Chemicals

Bulk pharmaceutical chemical processes are typically biochemical or chemical syntheses carried out on a relatively large scale. The bulk pharmaceutical chemicals may be provided to pharmaceutical manufacturers as active or inactive ingredients for eventual inclusion in a finished dosage form pharmaceutical. The bulk pharmaceutical chemical manufacturing process for active ingredients is typically enclosed in large tanks with direct transfer of materials from tank to tank after a particular chemical reaction has occurred. The initial stages of the bulk pharmaceutical chemical drug development are reminiscent of the chemical industry. At some point during the process, the manufacturer must, in accordance with CGMPs have identified a process step after which the process will strictly comply with the CGMPs.

Bulk pharmaceutical chemical production, due in large part to the scale of manufacture and its use of strong reagents and chemicals, is often performed in closed systems which may use automated or semi-automated Clean-In-Place technologies. The difficulties in the validation of cleaning processes often stem from the inaccessibility of many areas to direct sampling. The contaminants to be removed include precursor molecules, intermediates, byproducts, impurities or other physical forms such as isomers or polymorphs, which exist from early stages in the process.

Clinical Products
In this document, clinical products identify those products which are currently registered as an investigational status due to their involvement in clinical trials. The Clinical Products category identifies the special care that must be taken with these products which may not be as fully characterized as marketed materials. Both pharmaceutical and biopharmaceutical drug products and drug substances are included in this category.

Cleaning in a clinical manufacturing setting is often complicated by the use of small scale manually cleaned equipment. Clinical manufacturing may represent a period during which process improvements are made, and therefore the same equipment may not be used each time the product is made. Also, since clinical products are often manufactured in development facilities, the subsequent products may not be known. The next materials manufactured may be research products, development products, placebo products or other clinical products. Our intent is to address cleaning of equipment in Phase III and later, but it may be appropriate to consider the same approaches in earlier phases as well. Typically, assays for low level detection of the active ingredient and its excipients will need to be developed and validated. Verification of cleaning effectiveness, as opposed to traditional validation, is prevalent since information on the material is not readily available.

2. The Cleaning Continuum

The subject of cleaning validation is one which the pharmaceutical and biotechnology industries have struggled with. Progress to a consensus in approach in the industry has been slowed by the number and complexity of issues surrounding the cleaning process and the variety of facilities, products and equipment in use. The development of a universal approach to cleaning validation is unlikely given these variations.

2.1 Use of the Cleaning Continuum

The intent of this section is to describe the limits of the cleaning continuum (see Table 1). These limits represent the extremes in the range of operating differences found within the industry which preclude a uniform approach. At each end of the continuum, the cleaning validation requisites are either simple or complex. Recognition that there are many of these coupled limits, and that each cleaning process has a unique place within each level of the continuum, explains why specific industry-wide approaches have been so difficult to develop.

The cleaning continuum provides some of the primary points to consider in any cleaning validation program. The continuum helps firms to establish the parameters which are critical factors for individual products, thereby enabling them to set priorities, develop grouping philosophies and establish the "scientific rationale" which will govern the cleaning program. The continuum will assist in determining which processes, equipment and products represent the greatest concerns and may help to establish the criticality of cleaning limits and methods. The continuum should be used during the initial phases of defining a cleaning validation program or during new product development.

The cleaning continuum includes: cleaning program criteria, equipment characteristics, quality attributes of equipment design, formulation/product attributes, analytical methodology and manufacturing/process attributes. All of the factors in the continuum directly affect the ability to

clean; however, their relative importance and criticality may be different from one company to another.

Table 1: The Cleaning Continuum

Manual	Automated Cleaning
Clean-out-of-Place (COP)	Clean-in-Place (CIP)
Dedicated Equipment	Non-Dedicated Equipment
Product Contact Surfaces	Non-Product Contact Surfaces
Non-Critical Site	Critical Site
Minor Equipment	Major Equipment
Low Risk Drugs	High Risk Drugs
Highly Characterized	Poorly Characterized
Sterile	Non-Sterile
Solid Formulations	Liquid Formulations
Soluble	Insoluble
Single Product Facility	Multiple Product Facility
Campaigned Production	Non-Campaigned Production
Simple Equipment Train	Complex Equipment Train

2.2 Cleaning Program Criteria

When establishing a cleaning validation program, it is important to first characterize the types of cleaning that are used in the facility. The cleaning methods that are used in a facility can reveal important factors with regard to process control, process reproducibility, the best ways in which to challenge the process, the best ways in which to collect samples and the best ways in which to monitor cleaning effectiveness during routine cleaning.

Automated Cleaning 76 Manual Cleaning

Automated cleaning will usually provide reproducible results. Process control is inherent in automated systems and process monitoring is frequently integral with the control system. Automated systems may not adjust to present conditions. The validation of an automated system requires that the cycle is proven to be rugged and will provide reproducible results under a given range of operating conditions. Control system validation is a large part of the validation of an automated cleaning system.

Manual cleaning is a universal practice within the pharmaceutical industry. There are many pieces of equipment and portions thereof for which construction and/or configuration make manual cleaning a necessity. The control of manual cleaning is accomplished by operator training, well defined cleaning procedures, visual examination of equipment after use and prior to the next use, and well-defined change control programs. It may be desirable to identify worst case cleaning situations (in terms of operator experience and/or cleaning methodology) for validation purposes. With manual cleaning, concern must also be given to the ruggedness of the method. Successful reproducibility is a function of strict adherence to written procedures.

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Clean-In-Place (CIP) 76 Clean-Out-of-Place (COP)
The cleaning of large pieces of equipment may be performed in the equipment's permanent location, generally in a configuration very similar to that in which it is utilized for production. This procedure is widely known as Clean-In-Place (CIP). Smaller equipment items are frequently transported to a designated cleaning or wash area where the cleaning procedure is performed. This practice is known as Clean-Out-of-Place (COP), but the term is not as prevalent as its counterpart.

The additional activities involved with transport of equipment to and from the wash room, component identification, the elimination of cross-contamination potential during transfer, and cleaning and storage prior to use make the validation of COP procedures somewhat more difficult than the comparable CIP activity. The need for manual manipulation is an integral part of many COP procedures and requires detailed procedures and training. The manual manipulation makes COP concerns similar to those of manual cleaning in place.

The use of automated washing machines to COP smaller items is an important part of many COP systems. The use of these systems reduces the differences between CIP and COP significantly. These systems are considered to be highly reproducible in their cleaning performance and are gaining wide acceptance.

2.3 Equipment Characteristics / Materials of Construction

Equipment usage during production is another important aspect to consider in establishing a cleaning validation program. It is important to understand not only the range of products that are likely to come into contact with the various equipment surfaces, but also the role that the equipment plays in the production train. This will help to establish the contamination and cross-contamination potentials of the equipment.

Equipment design characteristics, as established during product development, are often driven by equipment functionality and the requirements of the process. With the current emphasis on cleaning validation, it makes sense that "cleanability" be a key criterion in the design of equipment.

Dedicated 76 Non-Dedicated Manufacturing Equipment
Dedicated equipment is used solely for the production of a single product or product line. Concerns over cross-contamination with other products are markedly reduced. Dedicated equipment must be clearly identified with the restrictions of use in order to prevent potential errors during cleaning and preparation.

Where the same piece of equipment is utilized for a range of product formulations, (i.e., non-dedicated equipment), the prevention of cross-contamination between products becomes the main objective in the cleaning validation effort. Clearly, cleaning non-dedicated equipment represents a more significant obstacle to overcome.

Dedicated 76 Non-Dedicated Cleaning Equipment
The issues of dedicated and non-dedicated equipment can also arise when considering the equipment used for cleaning. CIP systems, for example, are frequently used for many

different tanks in a single facility. Inherently, the design of CIP systems should preclude cross-contamination through appropriate valving and back-flow prevention. Care should be taken with shared devices which apply cleaning agents, such as spray balls or spray nozzles which, themselves, may require cleaning. Certainly any recirculation within the CIP system should be configured carefully during system design and monitored closely during routine operation.

COP equipment, such as an ultrasonic sink, may also be used for multiple equipment loads. With cleaning apparatus such as the sink, the removal of potential contaminants from the sink, itself is a concern. Sinks and washers frequently use recirculation systems to economically remove residuals from surfaces without undue waste. The cleanliness of the recirculated materials should be evaluated during cleaning validation to ensure that contaminants are not being redeposited on the equipment to be cleaned.

Non-Product Contact 76 Product Contact Surfaces
Traditionally, the validation of cleaning has focused on product contact surfaces. Programs for the elimination of cross-contamination must address non-product contact surfaces if they are to be truly effective. In practice, cleaning validation requirements may change with non-product contact surfaces in accordance with the less critical nature of these areas. When establishing the requirements for non-product contact surfaces, it is important to review the possible interactions of that area with the process.

Non-Critical Site 76 Critical Site
Critical sites are those locations in which a contaminant is in danger of affecting a single dose with a high level of contamination. Critical sites often require special cleaning emphasis. It may be appropriate to establish more intensive sampling schedules for critical sites, set tighter acceptance criteria for critical sites and ensure that enough detail is included in cleaning procedures to provide for reproducible cleaning of critical sites.

Minor Equipment 76 Major Equipment
The distinction between "major" and "minor" equipment is not a definitive one. The CGMPs make mention (211.105) of "major" equipment, but are silent on the subject of "minor" equipment except with regard to items described as utensils (211.67). Despite this failure within the CGMPs, it is necessary to identify those pieces of equipment (major) which are central to the production process and those pieces of equipment (minor) which perform a secondary role.

Typically the cleaning of "major" equipment will be the subject of individual, highly specific SOPs. In contrast, "minor" equipment and "utensils" are often cleaned using broadly defined procedures which describe the methods to be used in general terms.

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Materials of Construction

The materials of construction of the equipment should be considered carefully when establishing a cleaning validation program. The attributes of the surface to be cleaned will define the residue to surface interactions, identify possible contaminants and point to areas which may not be readily cleaned or accurately sampled. The CGMPs (211.65) state that,

"a) Equipment shall be constructed so that surfaces which contact components, in-process materials, or drug products shall not be reactive, additive or absorptive so as to alter the safety, identity, strength, quality or purity of the drug product beyond official or other established requirements.

"b) Any substances required for operation, such as lubricants or coolants, shall not come into contact with components, drug product containers, closures in-process materials, or drug products so as to alter the safety, identity strength, quality or purity of the drug product beyond official or other established requirements."

Equipment should not be reactive, additive or adsorptive with the process materials which contact them. The use of porous surfaces for multiple products should be avoided (filters, filter bags, fluid bed drier bags, membrane filters, ultra filters). Any surfaces which have these properties will require review during cleaning validation evaluations to ensure adequate product removal and minimize the potential for cross-contamination. The interaction of cleaning agents with surfaces that are likely to display these properties (e.g., seals, gaskets, valves) should be assessed.

2.4 Product Attributes

The cleaning of equipment is closely tied to the type of materials being removed from the surface. The product formulation is often the key in establishing appropriate cleaning acceptance criteria, challenge methods and sampling techniques.

Low Risk 76 High Risk Drugs

The residual limits utilized for cleaning validation are often closely related to the allergenicity/toxicity/potency of the materials in question. The limits are eased when the materials being removed are generally of lower pharmacological activity. At the other extreme, there are numerous materials and formulations, where even minute quantities can have pharmacological activity. The equipment and the procedures utilized to clean the equipment might be identical, yet the production of materials with known adverse effects may require that tighter limits be achieved. Cleaning, sampling and analytical methods may need to be refined to a high degree of sensitivity to ensure that the equipment has been properly cleaned.

Many firms have used dedicated facilities and/or equipment, or conducted cleaning verification in order to circumvent some of the inherent difficulties in processing high risk drugs. The difficulties of reproducibly demonstrating successful cleaning may make it operationally easier to dedicate the equipment and/or facility to the production of a single product rather than attempt to clean to the necessary level of cleanliness.

The route of administration of a product may affect the level at which the product is found to be allergenic, toxic or potent. Generally speaking, injectable products, intra-ocular formulations, and some inhalants which provide direct access to the systemic circulation systems of patients are a much greater concern in terms of cross-contamination.

Highly Characterized 76 Poorly Characterized

The introduction of pre-approval inspection requirements for NDA and ANDA approval has resulted in greater scrutiny being placed on documentation describing the development of the formulation. Regulatory agency expectations for cleaning validation are formidable within the confines of marketed product manufacturing (typically highly characterized products) but placing the same requirements upon developmental drugs (typically poorly characterized) makes cleaning validation even more difficult. During product development, the formulation, process and equipment to be utilized in production are evaluated in order to ensure a consistent process for commercial scale manufacture. Before the final equipment selections are made, however, a wide variety of equipment combinations may be tried, resulting in a vast array of cleaning combinations.

In addition to the myriad of cleaning processes which must be evaluated, there are additional difficulties: appropriate limits for active agents must be selected; this limit might be based upon a not yet identified therapeutic dose. Alternatively, using the lowest dose, or considering using the worst case might save time on scale up, provided that the appropriate assays for these levels have been developed and validated. Other difficulties include the requirement that appropriate analytical methods must be developed for all formulations. Clearly, while the validation of cleaning is a difficult task in a production facility, the unknowns inherent in clinical product manufacturing, where the product is poorly characterized, make the task even more challenging.

Other areas where products may be poorly characterized include bioprocesses and syntheses where vast numbers of related molecules may be formed, in addition to the primary product. While there are generally requirements that all of these potential "contaminants" developed during the manufacturing process be identified, these materials may not be characterized well enough to have specific, low-level assays developed for each of them. The establishment of appropriate limits for each of these substances is equally complicated and may not be feasible.

Non-Sterile 76 Sterile

The production of sterile formulations increases the extent of cleaning operations relative to non-sterile products. Sterile manufacturing facilities must control microbial, endotoxin and particulate levels to a degree not common with non-sterile products. Not only are the number of concerns increased but the nature of these contaminants makes the successful removal of these items (and their validation) more difficult. Sampling methods for these contaminants are more subjective, the analytical methods more demanding, and the validation generally more difficult to complete.

Concerns relative to microbial and particulate control are lessened in the production of non-sterile products but are still important. Practices which minimize the potential for

contamination by "objectionable organisms" are common in the manufacture of non-sterile formulations such as oral liquids and topical products.

2.5 Formulation Attributes

Attributes of the formulation have been identified in the section on residues (Section IV.)to have a great influence on the ability to clean. In general, solid and liquid formulations represent the range of physical product attributes and soluble and insoluble represent the ability of products within the continuum to react with the agents which are used to clean.

Solids 76 Liquids

The differences in the cleaning of equipment utilized for solid and liquid formulations are quite significant. The distinction between these formulation types is related to how contamination might be left on the equipment and dispersed in subsequent products. Liquid formulations may have greater ability to penetrate equipment seals and joints, hindering their removal. In contrast, solid formulations may have unique abilities to form aggregations of product. This "clumping" may inhibit "wetting" by cleaning agents thereby limiting the ability to "rinse" the residual product away.

The "distribution" of the contaminant is often considered to be quite different for solid and liquid formulations as well. Liquid products are often considered to have superior dispersion of active ingredients uniformly across surfaces, while solid products are expected to have more point to point variability, based primarily upon equipment configuration.

Soluble (Active or Excipient) 76 Insoluble (Active or Excipient)

Soluble products are often easily removed during cleaning by solubilizing the product, both active and excipient, so it can be "rinsed" away. Insoluble materials, on the other hand, will resist going into solution and must be removed by a more physical means or by the addition of cleaning agents that result in increased wetting, emulsification or solvation of the materials.

Some products may demonstrate both soluble and insoluble behaviors with the various raw materials which compose the final product.

2.6 Operational Issues

Operational issues such as the number of products manufactured, the use of campaigns and utilization of equipment and the complexity of the equipment impact the design of the cleaning validation program.

Single Product Facility 76 Multiple Product Facility

The circumstances surrounding a single product facility are analogous to those for dedicated and non-dedicated equipment. In those instances where a facility, which might be a separate building on a large site, produces only a single product, the validation requirements are simplified by the elimination of cross-contamination concerns.

Multiple product facilities (also referred to as multi-product or multi-use facilities) clearly represent a more difficult challenge. Procedurally, steps must be taken in a multiple product facility to ensure that cross-contamination potentials are eliminated. Change-over of equipment from one product to another must be carefully controlled. After cleaning validation is completed, monitoring programs may be warranted which ensure that all controls are in place and that limits established during cleaning validation are maintained.

Campaign Production 76 Batch Production
Within a multiple product facility, a production campaign may be utilized to minimize cross-contamination issues between lots. For campaign production, multiple lots of a single product or product family are produced in the same equipment. In some instances, it is deemed appropriate to interrupt this production run with what is sometimes considered a less stringent cleaning procedure and evaluation between lots. Once the campaign has been completed, the firm will perform an intensive cleaning of the facility and equipment before beginning the production of a different product.

In long campaigns, the potential for contamination or product residue build-up with time can result in concentrations higher than typical for a single lot. The repetitive production of a single product might also result in the penetration of materials into a location where single lot production might not present a problem.

Simple Equipment Train 76 Complex Equipment Train
An equipment train is generally recognized as a grouping of equipment or systems which function as a unit during the production of a product. The complexity of the "equipment train" is based on the number of discreet pieces along the train, the number of transfer or process steps and the ability to sample the equipment train as discreet items (e.g., closed systems). The complexity of the cleaning validation is directly proportional to the complexity of the equipment train.

3. Cleaning Validation

3.1 The Cleaning Validation Program

Frequently, the basis of cleaning validation programs is the establishment of a plan which describes the overall validation approach. The rationale for any grouping philosophies utilized and the validation program to be implemented should be identified.

After the determination has been made of which product(s) and piece(s) of equipment are to be utilized in the validation study, the validation trials may commence. If the product is to be coated on equipment surfaces to form a trial for cleaning validation, care must be taken that the product coverage used for validation is appropriate to simulate the level of contamination that would be present in an actual manufacturing situation.

Care should also be taken in the simulation of the production methods utilized. For example, a piece of equipment that is utilized first thing in the morning may sit, contaminated with product, until the second shift starts. Having the product "dry" on the equipment, therefore, may be the worst case.

It is important to consider the effect that weekends, holidays and delays might have on the cleaning schedule. It is advisable to determine the stability of material remaining on equipment for longer time periods than in a normal manufacturing sequence. Material typically may degrade, dehydrate or may strongly adhere to equipment after long time periods. It may be advisable to establish the stability of the product in the manufacturing equipment for the longest (i.e., worst case) holding period. Regulatory inspectors are known to be quite interested in how the company has taken the stability and cleanability of materials into account when materials sit in equipment for long periods of time. The product reserved in the open container should be evaluated for product degradation studies. The validation group, user group, quality assurance group, etc. are all responsible for ensuring that the test program is an accurate reflection of actual production.

The cleaning of the equipment should proceed in accordance with the documented standard operating procedure for cleaning. After the cleaning has been completed, an intensive sampling of the system may begin. (See the section on Sampling Techniques and Analytical Methods.) Attention should be given to product contact areas, intricate areas, and critical sites. As defined previously, critical sites are those locations in which a contaminant is in danger of affecting a single dose with a high level of contamination.

The number of trials to be performed for each system is another issue which is often debated. Most cleaning validation programs demonstrate the reproducibility of a process by three (3) consecutive trials for a single product on a single piece of equipment. If a firm chooses to pursue the grouping philosophies for the initiation of the cleaning program, it may be part of the plan to pursue the representative products and equipment with three (3) trials each. After completion of the trials which were "representative" of the most challenging cleaning, it may be appropriate to reduce the number of trials for subsequent products which fit within the grouping baseline. If reducing the number of trials to be performed, great care should be taken to identify the rationale for the product grouping and to demonstrate the equivalency of new findings to the initial results.

3.2 Product Grouping

Many companies seek a common denominator whereby similar products may be “grouped.” Through this process, the company attempts to convert a complex situation into a manageable project. Typically, products are first grouped according to formulation and dosage form, including considerations of potency, toxicity and solubility. These product groupings are further subdivided by types of equipment used in their manufacture. Further distinctions are made according to cleaning method and agent.

A common basis for grouping is by product. The grouping is usually based on the formulation or the dosage form of the product. When this approach is used, the company’s products are divided into groups according to the dosage form and then according to formulation. For example, a company might have 10 tableted products, 6 ointment products, and 4 liquid products. In this case, the first evaluation would be that the products fall naturally into 3 broad groups. However, if 6 of the tableted products were manufactured by a wet granulation process, whereas 4 of the products were manufactured by a dry, direct compression method this would be a basis for subdividing the tablet group into 2 subgroups. Likewise, if 2 of the liquid products were suspensions and the other 2 liquid

products were true solutions, this would also create 2 subgroups for this group. Thus, the hypothetical company would actually have 5 groups of products for cleaning validation purposes.

Once the product groups have been established, the next step is to determine the so-called "worst case" representative of each group. This may be done according to toxicity, solubility or the presence of ingredients known to be difficult to clean, such as insoluble dyes. There is no "hard and fast" rule for this selection. In some cases, a combination of these parameters may be used. For example, if a group consisted of 5 products, four of which were cough/cold formulations and the fifth a cytotoxic product, then the cytotoxic product would be a logical choice as the worst case product.

Another example would be a group composed of 8 products of similar potency. In this case, the worst case selection might be made on the basis of solubility. Again, the choice of the least soluble product in the group as the worst case product would be easy to defend.

A third example might be the group composed of several products having the same active ingredient and differing only in the concentration of the active ingredient. In this case, it would be reasonable to select the product having the highest concentration of active since this product would present the greatest cleaning challenge.

As these examples illustrate, the most important aspect of the grouping is the preparation of a logical and scientific rationale justifying the grouping and the selection of the worst case representative. In certain cases, a clear cut worst case may not emerge. In those instances, it may be appropriate to select two or more "worst cases" to represent the group.

It is unlikely that a single worst case product could apply to an entire line of products having significantly dfferent formulations and dosage forms.

3.3 Manufacturing Equipment Grouping

Companies may choose to selectively perform cleaning validation studies on representative groups of equipment. For equipment groupings, form and function define the criteria for the grouping philosophies. Equipment which is similar in design and function, perhaps differing only in scale, may appropriately be grouped when performing validation testing. Throughout the validation studies, however, scientific principles must be followed. The cleaning method may be validated on the largest and smallest scale equipment within the grouping if the same cleaning procedures are to be implemented.

When establishing priorities of the equipment to be tested, it is important to evaluate the function of the equipment. Major process equipment should be included in any cleaning validation program. Major process equipment, which can be defined as having a unique identification or asset number, is often the first priority. Minor equipment, such as utensils, small parts, and smaller equipment may be validated separately. In the case of minor equipment, it may be appropriate to evaluate a cleaning procedure for miscellaneous parts and attempt to validate the range of small parts in terms of complexity and size.

3.4 Cleaning Method Groupings

As mentioned in the discussion of utensils and small equipment, it may be appropriate to group cleaning studies based upon the utilization of a single cleaning method. The validation of the cleaning procedure may be conducted almost independently of the equipment for which it is used. As long as the range of equipment configuration and product formulation are used to challenge the cleaning method, this grouping, when scientifically applied, is as appropriate as any of the other grouping philosophies.

3.5 Cleaning Agent Groupings

The use of a single cleaning agent will greatly reduce the work required to determine if residues of the agent remain after cleaning. For multi-product facilities, it may be necessary to use several different agents to remove the various types of excipients that are present in different products. When considering the product formulation and equipment groupings, it is appropriate to also consider and subdivide systems based upon the cleaning agents utilized on those systems. The agent grouping should display analogous profiles in the ability to remove similar product formulations if all other cleaning method variables are the same. Care must be taken to ensure that worst-case products are chosen. Typically, this approach is best if used in combination with other groupings.

Groupings should help to develop baseline data on which to establish the ongoing validation program. New products should be added to the grouping or tested if they fall outside of the established baseline.

4. Residues and Residue Removal

High levels of residues from manufacturing, packaging and cleaning procedures can lead to product contamination. The purpose of validated cleaning procedures is to ensure that potential contamination is consistently removed from the manufacturing and packaging equipment and contamination is prevented.

4.1 Types of Residue

When establishing a cleaning program, it is important to first identify the substance to be cleaned. Residues have physical and chemical properties which will affect the ease with which they are removed from surfaces. Degree of solubility, hydrophobicity, reactivity and other properties will affect the characteristics of these residues during the cleaning process. The type of cleaning and cleaning agents to be used must be chosen carefully according to the chemical and physical properties of the residues to be removed.

4.2 Cleaning Agents

Cleaning agents, such as detergents, often aid in the physical removal of residues from surfaces. Simple water rinses may be adequate to effect the removal of highly soluble materials, but may not work as well with insoluble materials or those with a combination of properties. In these cases, agents can be selected which assist in the removal of residues. Alternating acid and base rinses is

especially effective for removing certain proteins.

When cleaning agents are used to aid the cleaning process, it is important to remember that their removal must be demonstrated (i.e., validated). For this purpose, it is necessary to know the ingredients contained in the cleaning agent. The cleaning agents are multi-ingredient products and often the supplier considers the formulas proprietary or trade secrets. In most cases, the supplier should divulge the ingredients, but may not disclose the amounts or composition of the cleaning agent formulation. Material Safety Data Sheets (MSDSs) are essential. Once the ingredients are known, the company must then determine the worst case ingredient in the cleaning agent. Fortunately, most suppliers of pharmaceutical cleaning agents use only materials that are water soluble and removal of the cleaning agent is not a problem. However, this can not be assumed and must be demonstrated by actual validation of the removal process, whereby samples are taken, analyzed and compared to pre-determined limits.

4.3 Microbiological Contaminants

Certain formulations such as parenterals, ophthalmics, semi solids, oral solutions and topicals may require control of microorganisms prior to further processing. In these instances, product contact surfaces should be evaluated for microbial contamination in conjunction with the overall cleaning validation program.

Sampling and enumeration methods used for environmental surfaces may be readily adapted for this purpose.

Microbial limits are established based on the route of administration and the nature of the product itself (biocritical, hostile, etc.). In addition to numeric limits, consideration should be given to ensuring the absence of specific, objectionable organisms based on the nature of the product (S. aureus, E. coli, and Pseudomonas sp.)

For parenteral products, similar controls are necessary to limit the amount of endotoxins on product contact surfaces.

Control of microbial contamination for other dosage forms and processes may also be appropriate.

4.4 Other Contaminants to be Removed

When examining equipment for types of residue, it is important to remember that the equipment itself should not contribute contaminating agents. Lubricants, surface coatings and sealants must all be reviewed during the equipment design so that they present no danger in leaving behind residues that will adulterate products. For sterile products, the operation of the equipment during cleaning should not generate particulates. In keeping with CGMPs, equipment must be non-porous, non-reactive, non-additive and non-adsorptive.

For non-aqueous processes where water is used in cleaning, it may be necessary to validate post-cleaning drying periods. The presence of residual water after cleaning may result in microbial or endotoxin contamination.

4.5 Cleaning Agent and Surface Interactions

It is important to consider potential interactions that the cleaning agents may have with the equipment surfaces. Glass, stainless steel, ceramic, plastics and various synthetics fibers may interact differently with cleaning materials.

5. Cleaning of Equipment

The cleaning processes used in our industry rely upon solubilization, chemical reaction and physical action for residue removal. It is possible to optimize the solubilization of the drug and still not achieve clean equipment. Often the physical action associated with cleaning and the disassembly of the equipment determine the success of the cleaning process.

A number of variables should be taken into consideration when designing equipment and in the development and performance of the cleaning process. These variables include but are not limited to the equipment surface characteristics, equipment geometry, equipment composition, the cleaning agent, temperature and flow rate of cleaning agents and time of exposure. For manual procedures, other factors, such as the detailed steps of the cleaning process and operator training, play a large role. In both manual and automated cleaning, the disassembly of equipment may be necessary for effective, reproducible cleaning.

5.1 Types of Cleaning Processes

Three broad definitions of cleaning processes follow. The distinctions between these processes is critical to the establishment of an appropriate cleaning validation program.

Manual

Manual cleaning is typically defined as the direct cleaning of equipment by a trained equipment operator using a variety of hand tools and cleaning agents. Although some process parameters may be monitored by gauges, the regulation and control of these parameters is the responsibility of the operator.

Critical cleaning parameters for manual cleaning may include: the volume of cleaning agents, volume of rinse water, temperature of wash and rinse solutions, duration of wash and rinse cycles, pressure of solutions, and detergent concentration. It is important to specify in writing the extent of the equipment disassembly to ensure the reproducibility of the cleaning process.

In a manual cleaning validation program, the critical factor is the ability to provide a reproducible process. The control of manual cleaning is accomplished by operator training, well defined cleaning procedures, visual examination of equipment after use and prior to the next use, and well-defined change control programs. One benefit of manual cleaning is that the operator is cognitive and able to adjust to and report changing conditions.

Semi-Automated

As opposed to manual cleaning, semi-automated cleaning includes various levels of automatic control. At one extreme this could consist of simply manually removing gaskets/fittings for

manual cleaning prior to automated CIP of a tank or disassembly of a pump prior to cleaning in an automated COP system. At the other extreme, the operator may use a high pressure spray device to clean a surface or may simply open and close water valves supplying spray balls inside a vessel. This level of cleaning approaches the definition of manual cleaning but often requires more sophisticated equipment to assist the operator.

Automated

Automated cleaning typically does not involve personnel intervention. The system is usually programmable for the various cleaning cycles. These types of cleaning systems provide consistent cleaning due to the automation of the process.

Critical cleaning parameters for automated cleaning may include the volume of cleaning agents, volume of rinse water, flow rates and temperature of wash and rinse solutions, duration of wash and rinse cycles, pressure of solution, operating ranges and detergent concentration. Disassembly of equipment may still be necessary to allow for complete cleaning or to allow for the separate cleaning of delicate parts.

In an automated cleaning system, the cleaning may be controlled through relay logic, a computer or PLC (Programmable Logic Controller). The control system is an integral and critical part of the overall cleaning process. The control system regulates the cleaning cycles, addition of cleaning agents, temperature, time and other critical cleaning parameters.

There may also be a control interface or operator interface to start the process, stop the process, monitor various stages of the process and change the process sequence. Given the increased complexity of the newer PLC and computer interfaces, training and validation are important issues that impact the ability of the system to provide consistent cleaning. The validation of control systems and the change control policies which govern them are critical to the success of the cleaning process.

5.2 Clean-in-Place (CIP) Systems

The term "Clean-in-Place" generally refers to an automated system that consists of a recirculation system which uses various tanks and a return system such as an educator or return pumps. A system of piping delivers the cleaning solution to the equipment and returns it to a motive or recirculation tank. There is usually a pre-rinse tank and a final rinse or purified water rinse tank. The equipment utilizes spraying devices to provide coverage and physical impingement of the cleaning solution of the equipment surfaces. The spray-balls may be stationary or moving (e.g., rotating, oscillating). These systems are commonly used to clean large pieces of equipment such as manufacturing tanks, blenders, fluid bed dryers, reactors and fermentation tanks. The CIP system need not have a recirculation system, i.e., it may be a single pass system where appropriate.

When cleaning solutions are recirculated and reused, it is important to assess their suitability for subsequent use. Continuous flow systems must ensure that there is no possibility of "backflow" to previous steps in the process.

Bulk pharmaceuticals are typically manufactured within closed systems increasingly equipped with automated or semi-automated CIP equipment. The mechanical qualification of flow rates, pressures, and spray ball patterns must be established.

5.3 Clean-Out-of-Place (COP) Systems

Clean-out-of-place equipment includes such items as wash tanks used to clean small parts or parts removed from large equipment. These systems usually have some sort of automated or programmed control system. One example is a recirculating bath used for cleaning small parts, pump components, gaskets and other parts removed from larger equipment. Clean-out-of-place systems may also include dishwasher type cabinets where small manufacturing vessels, drums or hoppers can be loaded inside the cabinet and cleaned. The placement of the parts, disassembly of equipment and loading are critical to the success of cleaning when using clean-out-of-place systems.

5.4 Cleaning Porous Equipment

The cleaning of porous equipment is a concern due to the ability of the surface to absorb drug. In this case, dedication of the equipment would be the preferred choice. If the porous equipment or part cannot be dedicated, then cleaning procedures for soaking the material in a solvent or extracting absorbed drug may be required. In these cases the sampling practices may need to be more stringent to ensure that absorbed drug and/or residual impurities are removed during the cleaning process.

5.5 Disposable Equipment

Use of disposable or single use equipment or components such as hoses, filters and scoops can be considered in lieu of cleaning when cleaning may be difficult to accomplish or demonstrate. Pre-use cleaning or flushing may be necessary to minimize extractables or particulates. Appropriate use and control procedures should be in place.

5.6 Placebo Batches as a Cleaning Method

It may be feasible to use a placebo run as a method of cleaning equipment. However, this approach is costly and requires the use of a placebo that has no detrimental quality impact on the next product manufactured using the equipment. The principle of using a placebo batch to effect cleaning is that the abrasive action of the placebo running through the equipment would clean the equipment of drug residues or process residuals from the previous batch. The advantage for this type of cleaning is that the placebo is processed through the equipment in the same fashion as the manufactured product and therefore the material would touch the same surfaces and in the same manner as the next product batch. Regulatory agencies have expressed concern over the effectiveness of this method.

5.7 Residue Removal and Cleaning Methods

As identified previously, cleaning relies upon the solubilization, chemical reaction and physical action for removal of residuals. Some of the methods for achieving residue removal in these categories include: dissolving, suspending, emulsifying, sequestering, wetting, saponifying, and scraping, brushing and scrubbing.

The effectiveness of a cleaning agent when in contact with the residue that is to be removed may be dependent upon such parameters as the cleaning agent concentration, exposure time, pressure, temperature or pH.

Often the interactions of the cleaning agent and the process residue are not enough to result in effective cleaning. In these instances, additional techniques such as agitation, direct impingement, and disruption by ultrasonic vibration have proven useful to facilitate residue removal.

The determination of the cleaning cycle will depend upon equipment design criteria, surface characteristics, geometry and composition. The equipment design criteria will affect the amount of residual remaining on equipment surfaces and the ease with which such residuals are removed. In most types of cleaning, some disassembly of the equipment may be required. Disassembly is critical in providing access to previously inaccessible areas of the equipment as well as providing the opportunity to visually examine the internal surfaces to verify that they have been effectively cleaned by the cleaning process. It is important to include disassembly directions in the cleaning SOP and training activities to ensure reproducibility of cleaning.

5.8 Equipment

The equipment utilized for performing the cleaning operation, whether a simple sink or a complex CIP system, must be well characterized as to its operational components. The design of the equipment should be appropriate to the system or parts to be cleaned.

There are certain equipment locations that are especially difficult to clean. When reviewing the configuration of the equipment, it is possible to identify potential critical sites or areas where residues are likely to accumulate. Thorough sampling of equipment during the execution of the cleaning cycle development, particularly selective sampling which targets specific areas throughout all steps of the cleaning process will help to identify these locations. Filler needles or tablet punches are examples of sites which, if contaminated, could potentially affect a single dose. Convoluted or difficult to clean equipment and locations may also contribute a large dose of contaminant. Sampling procedures and limits should be considered carefully if an accurate determination of the ability to clean these locations is to be made.

In continuous process trains, it may be desirable to isolate portions of the equipment or system in order to provide more effective cleaning. In these instances, the location of all isolation points and their design are critical to ensuring that the interfaces between the sections are appropriately cleaned.

5.9 Equipment Design Considerations

Equipment cleanability and function must be considered during equipment design. In order to minimize the risks of cross-contamination, microbial or endotoxin contributions to equipment, the system must be designed with care. This applies to process equipment and the cleaning process itself.

Ideally, the equipment should be constructed of non-reactive, non-additive, non-adsorptive, non-porous materials. A review of the materials of construction may be warranted based upon the action of the cleaning agents to be used; if the cleaning agents are corrosive or are likely to react with such

components as sealants, plastics or filters, care should be taken when specifying design requirements and preventative maintenance procedures.

Equipment should be free-draining and have limited intricate or complex parts. Sanitary designs employing principles such as appropriately finished surfaces, lack of crevices, absence of dead legs and suitable construction materials are recommended.

Cleaning equipment should be designed to ensure adequate coverage of all process equipment surfaces to be cleaned. In tankage and enclosed piping systems, the volume of cleaning solution available must be sufficient to clean all interior surfaces of the pipe. For spray ball or nozzle spray apparatus, all equipment surfaces should be available for contact with the spray. The concern here is that areas can be "shadowed" by the presence of dip tubes and mixer shafts.

5.10 Cleaning Frequency

The frequency and rigor of cleaning is usually determined by the nature of the changeover process. For example, the frequency will depend upon whether the manufacturing involves many different products or several batches of the same product.

Between batches of different products
When equipment is changed over from one product to another, cleaning must take place to prevent product cross-contamination.

Between batches of the same product (campaign)
The cleaning frequency within batches of the same product should be determined as part of the process development. In some cases, it is possible to show that cleaning between batches may be reduced or eliminated. Validation should be accomplished to determine the number of lots of the same product that may be consecutively manufactured before a more rigorous cleaning is necessary.

5.11 Post-Cleaning Equipment Storage

After cleaning is completed, the equipment should be protected from cross-contamination due to the presence of other products or processes in the area. This involves covering the equipment or placing it in an area that is free from possible cross-contamination and designated for cleaned equipment. Visual inspection of the equipment immediately before use is necessary.

Major manufacturing and cleaning equipment should be identified with an appropriate equipment identification number. Records must be kept showing the equipment numbers, the date of the cleaning, who cleaned it and who inspected/tested it.

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5.12 Monitoring Cleaning Cycles

Temperature, flow, pressure, fluid level, drainage, conductivity and pH may play a role in monitoring the cleaning program. The nature of the cleaning method will determine the critical parameters to be monitored during cleaning. Critical operating parameter ranges should be established during cycle development and cleaning validation studies.

Instrumentation for monitoring critical parameters should be accurate and subject to a routine calibration program. Instrumentation may be placed directly in the process/cleaning stream or off-line for monitoring purposes. In-line instrumentation should be of appropriate sanitary design to prevent product or cleaning agent build-up and prevent "dead legs."

6. Cycle Development

Validation considerations for new products and existing product lines have both fundamental differences and similarities. Both may require cycle development and optimization activities prior to validation. They both may also require the development and validation of low level analytical detection methods for the active ingredient, detergent or cleaning solvent, and possibly excipients.

For new products, the cycle development and optimization steps are more readily accomplished in the process development phase. At this point the choice of detergent or solvent can be readily made. Critical data such as solubility, conductivity, and pH of the active in the detergent or solvent can be easily developed. Such data can be helpful in the design and development of the process and equipment for the production scale.

All critical monitoring instrumentation such as thermocouples or RTDs, pressure gauges, flow meters, conductivity sensors or pH meters must be identified and calibrated. The function of each monitoring device must be clearly understood. This is particularly true in an automated system, where individual devices may have a controlling influence over particular phases of the process. When specifying equipment to be used for cleaning, it is helpful to select equipment with multiple monitoring devices as they help to establish a reproducible cleaning process. All personnel must be trained and each operator must understand the cleaning steps and process.

In order to establish a validated cleaning procedure, whether manual, semi-automated or fully automated, it is generally useful to perform cycle development studies in order to establish the parameters which are to be validated. Proper development of the cleaning cycle provides confirmation of the safety of the process, economic savings, confidence in the validation starting point and experience with the test and sampling methods. At the conclusion of cycle development, it is possible to finalize standard operating procedures (SOPs) for the correct operation and monitoring of the cleaning system. The critical factors which influence the cleaning cycle to be developed include: the equipment, the cleaning agents, cleaning parameters, product or formulation, cleaning procedures, documentation and training.

It is important not only that operator training occur, but also that the training be well documented. Without proper documentation, it is impossible to prove that the training was actually accomplished.

Operators should be retrained each time a cleaning procedure is changed and the new training must be documented, just as in the case of a change to a manufacturing procedure.

6.1 Cleaning Agent Selection

The development of a scientific rationale should apply to cleaning agent selection and limit determination in much the same way as it applies to product cleaning program development. Cleaning agents should be selected for their suitability to remove the product residues and for low toxicity. Detergents, rinsing fluids and cleaning agents should be acceptable to the process and for use with pharmaceutical products. The acceptable limits for cleaning agent residues should be established using scientific rationale in much the same way as the limits for product residues are established.

At the time of prevalidation, it is important to review and document information about the cleaning agents. The established cleaning agents should be reviewed against the vendor's current specification sheets and descriptions. Those documents should be available as a minimum requirement for use of those cleaning agents before evaluating the cleaning process.

When selecting a new cleaning agent or utilizing an established cleaning agent for a new process, it is important to know all of the ingredients which are in the cleaning agent, along with the percentage each constituent comprises because the cleaning agent removal must be proven. If the cleaning agent proves to be the hardest residue to remove from a system, a new cleaning agent or formulation of cleaning agent should be sought.

Cleaning agents and their vendors should be qualified in much the same way as a raw material and raw material vendor is qualified. Change control of the cleaning agent formulation should be required of the cleaning agent vendor.

During the development of the cleaning cycle, quantities of cleaning agents, their concentration and their addition rate must be studied. Methods of storage, expiration dating, inventory control, and change control of the cleaning agents will help establish and maintain a reproducible process.

Water used to prepare cleaning agents and for equipment rinse should be of suitable quality. Generally, water used for final rinse should be the same grade used for the manufactured product, e.g., parenteral products should utilize WFI, oral products would employ purified water.

6.2 Product Considerations

Chemical and physical attributes of the product should be taken into account when establishing a cycle development program for a specific product. Characteristics such as the solubility, concentration, physical properties of the active and excipients, possible degradation products and the effect of the cleaning agent are critical factors in establishing that the cleaning method is appropriate. The interaction of the product with all surfaces with which it will come into contact is critical.

6.3 Cleaning Parameter Selection

As mentioned under Equipment Design Considerations (see Section 5.9), the best way to establish a reproducible process is to monitor and control critical process parameters. These cleaning parameters can be defined during the cycle development phase. The four widely accepted process parameters of time, temperature, cleaning agent concentration and cleaning action (impingement, sheeting, rinsing, etc.) are critical to the control and reproducibility of the cleaning processes. Each cleaning step can be evaluated to determine the reduction of contamination. The results will determine whether there is a need to add, delete or modify a cleaning process step.

Appropriate cleaning action at the product contact surfaces is required to ensure that residues are effectively removed. Differences in residue solubility will determine the optimum levels of impingement, sheeting, soaking and rinsing. Coverage (the inclusion of all surfaces for cleaning) is difficult to monitor and control but directly affects cleaning effectiveness. Some systems such as spray balls, will allow for highly reproducible coverage, provided that other variables such as pressure, timing and sequencing are closely controlled.

6.4 Standard Operating Procedures

Standard Operating Procedures should be developed in conjunction with the cleaning development phase. Draft SOP's should reflect sufficient detail to insure process consistencies. After the cleaning process has been validated, final standard operating procedures for cleaning should be highly detailed (e.g., time, temperature, concentration and cleaning action). This is particularly true for manual processes where the description of the cleaning process is critical to maintaining consistency of cleaning.

The maximum allowable hold time for a piece of equipment:

- after use before cleaning,
- after cleaning before reuse or recleaning,
- and, if appropriate, after cleaning before sanitization

should be validated.

The following should be validated, documented and included in the appropriate SOP:

- Extent of disassembly of equipment. Disassembly should be such that the equipment is broken down in a manner that will allow all parts to be effectively cleaned.
- Visual inspection for equipment wear, excessive product residuals and foreign materials.
- Critical sites or difficult to clean areas that may require special cleaning emphasis or a specific inspection.
- Assignment of responsibility for cleaning equipment.
- Cleaning schedules, and where appropriate, sanitizing schedules.
- A description in sufficient detail of the methods, equipment, and materials used in cleaning, and the methods of disassembling and reassembling equipment as necessary to ensure proper cleaning as well as the cleaning /handling and storage of tools used in cleaning (post cleaning).
- Removal or obliteration of previous batch identification.
- Protection of clean equipment from contamination prior to use.
- Inspection of equipment for cleanliness immediately before use.

6.5 Cleaning Records

During the cycle development phase, appropriate cleaning validation records and documentation are established for use in routine practice. These documents serve as the record of cleaning and demonstrate that the cleaning of the equipment will be checked by an independent reviewer.

6.6 Operator Training

Operator training is critical, especially for manual cleaning. During cycle development, operators should be trained in the requirements of the evolving or existing SOP's. Proper training consists of understanding the SOP, apprenticeship with qualified, trained operators and review to ensure that the training is successful. The effective training or qualification of the operators may be confirmed by monitoring of the equipment after cleaning, including, where necessary, analytical testing for residuals.

Training practices will vary from one company to another but operator training may be enhanced by some of the following suggestions:

- Clearly written, understandable and sufficiently detailed SOPs.

- Use of checklists to determine that all operations are carried out in the proper sequence and are documented.

- Periodic monitoring of cleaning processes to ensure proper training of operators and continued compliance with SOPs.

- Dedicated or assigned cleaning personnel.

- Feedback from operators to modify procedures.

- Use of video to demonstrate proper cleaning operations and techniques.

Overall the operators should understand the process of cleaning and the operation of the equipment they are cleaning. In addition the operators should be aware of the cleaning process impact on the quality of the next product manufactured in the same equipment.

7. Sampling Techniques and Analytical Methods

The presence of residues and microbial contamination can adversely affect the quality of the pharmaceutical product. Validated cleaning procedures will help prevent the potentially serious consequences of cross-contamination of products. In order to evaluate a cleaning method, it is necessary to sample the product contact surfaces of the equipment and establish the level of residuals present. The choice of sampling and analytical methods will depend upon the nature of the residue and manufacturing equipment.

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A sampling diagram should be prepared that indicates the actual locations to be sampled. These locations should include the worst case, most difficult to clean locations. Companies have used various approaches to depict the sampling locations such as CAD diagrams, engineering blueprints or simple diagrams, and even photographs, for this purpose.

7.1 Sampling Techniques

Regardless of the sampling technique chosen, it is appropriate to verify the recovery levels that are possible with a given sampling and analytical method. The objective should be to establish a reproducible level of recovery from the equipment surfaces. Standards of known concentration should be used to calibrate the assay in conjunction with the sampling. It is critical to test the sampling technique, in conjunction with the chosen assay method to ensure that accurate results are obtained.

Swabs and Wipes

Swabbing is a widely used sampling technique. Swabs may be saturated with solvent (e.g., water, alcohol), aiding the solubilization and physical removal of surface residues, or used dry.

Advantages:

- dissolves and physically removes sample
- adaptable to a wide variety of surfaces
- economical and widely available
- may allow sampling of a defined area
- applicable to active, microbial, and cleaning agent residues

Limitations:

- an invasive technique that may introduce fibers
- results may be technique dependent
- swab material and design may inhibit recovery and specificity of the method
- evaluation of large, complex and hard-to-reach areas difficult (e.g., crevices, pipes, valves, large vessels)
- subject to the vagaries of site selection

Rinse Sampling

Rinse samples (using the normal cleaning solution) can be evaluated at intervals during the cleaning and at the completion of the cleaning process. Collection of rinse samples should consider location, timing and volume.

Advantages:

- adaptable to on-line monitoring
- easy to sample
- non-intrusive
- less technique dependent than swabs
- applicable for actives, cleaning agents and excipients
- allows sampling of a large surface area

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- allows sampling of unique (e.g., porous) surfaces

Limitations:
- limited information about actual surface cleanliness in some cases
- may lower test sensitivity
- residues may not be homogeneously distributed
- inability to detect location of residues
- rinse volume is critical to ensure accurate interpretation of results
- sampling methodology must be defined since rinse sampling method and location can influence results
- may be difficult to accurately define and control the areas sampled, therefore usually used for rinsing an entire piece of equipment, such as a vessel
- reduced physical sampling of the surface

Coupon Sampling
Coupons of the same materials of construction as the item to be cleaned can be affixed to the equipment, spiked with the product, subjected to the cleaning procedures and then submitted to the laboratory for direct analysis and recovery studies.

Advantages:
- spool pieces can be effectively used for this purpose in fluid and powder handling
- allows for direct surface sampling with an analytical method
- non-technique dependent
- useful in cleaning development
- reduces variability in recovery
- useful in evaluation of equipment materials of construction

Limitations:
- coupon may not see representative contamination or cleaning because it may be separate from primary surface
- invasive
- might interfere with the cleaning process
- subject to the vagaries of sample site selection

Solvent Sampling
This technique uses a solvent not normally employed in the cleaning process to maximize recovery of expected residues. The solvent sampling technique entails the application of a known volume of solvent to the surface in question. The applied solvent is then collected and an aliquot sampled for the desired analytes. Solvent sampling is particularly appropriate for large pieces of equipment and can be used in combination with swabbing.

Advantages:
- commonly used in bulk chemical facilities
- applicable for actives, cleaning agents, excipients
- less technique dependent than swabs
- usually affords more analytical specificity, less recovery loss than swabs

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- allows sampling of a larger surface area
- allows sampling of unique (such as delicate or porous) surfaces
- maximizes recovery relative to rinse sampling

Limitations:
- may require operator protection and other safety and environmental protection measures
- may require more than one sampling for broad spectrum analysis
- reduced physical sampling of the surface
- some technique dependency
- may be difficult to accurately define the controlled area sampled, therefore usually used for rinsing an entire piece of equipment such as a vessel
- may require removal of the solvent prior to use

Product Sampling
Product sampling is similar to placebo sampling except that it uses actual product. It requires close examination of next production batch for trace residuals of the previous batch.

Advantages:
- the next product contacts the same surfaces as the previous product
- applicable for hard-to-reach surfaces
- requires no additional sampling steps

Limitations:
- difficult to determine recovery
- lowers analytical specificity and inhibits detectability
- residues may not be homogeneously distributed
- no direct measurement of residues on product contact surfaces

Placebo Sampling
Placebo sampling can be used to detect residues on equipment through the processing of a placebo batch subsequent to the cleaning process. It is appropriate for active residue, cleaning agent, particulates and microbial testing. Placebos are used primarily to demonstrate the lack of carryover to the next product. The placebo should mimic product attributes. The equipment characteristics also impact the choice of the placebo batch size.

Advantages:
- placebo contacts the same surfaces as the product
- applicable for hard-to-reach surfaces
- requires no additional sampling steps

Limitations:
- difficult to determine recovery (contaminants may not be evenly distributed in the placebo)
- lowers analytical specificity and inhibits detectability
- takes longer and adds expense since equipment must be cleaned after the placebo run
- placebos must be appropriate for each potential product

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- residues may not be homogeneously distributed
- no direct measurement of residues on product contact surfaces

Direct Surface Monitoring
Direct surface monitoring is used to evaluate surface cleanliness without surface contact, e.g., measurement using bioluminescence and spectrophotometric probes.

Advantages:
- rapid
- non-invasive
- economical

Limitations:
- subjective
- some techniques not widely developed or available (still experimental)

7.2 Visual Examination

Organoleptic techniques (i.e., visual, smell, touch) may be used as a component of the cleaning program and, additionally, as one of the tests useful for the validation of the cleaning procedure.

Visual examination of equipment for cleanliness immediately before use is required by the CGMP regulations. Visual examination is a combination of sampling and analysis, where the observer makes an immediate determination of equipment cleanliness. Visual examination of equipment, in particular, is utilized by the majority of pharmaceutical companies both as a means of evaluating cleaned surfaces during the cleaning validation stage and after cleaning validation is complete as part of an ongoing monitoring of the cleaning process. In some instances this method has been shown to have a high sensitivity.

The visual examination of equipment can be enhanced by simply passing an ultraviolet "black" light over the surfaces of the equipment. This use of an ultraviolet light would be effective for residues which fluoresce when irradiated with ultraviolet light. Another means of visual enhancement is the use of dyes which form colored complexes with certain residues such as proteins producing a colored residue much easier to observe visually than the uncomplexed free residue. For example, methylene blue can detect anionic detergent residues and proteins remaining on equipment.

Advantages:
- economical
- fast
- quantitative limit may be possible
- complies with a CGMP requirement
- sensitive
- long history of satisfactory results

Limitations:
- subjective

- may require disassembly

7.3 Relationship of Analytical Method, Sampling Method, and Limit

The selection of an evaluation method for determining whether equipment is clean does not focus solely on the analytical method; the sampling method and limits must also be considered. The testing and analytical methods chosen for a specific cleaning situation will be greatly influenced by the type of sampling method employed. Evaluation of these relationships must cover the sampling method, analytical method and the residue limit. and evaluation process, including the efficiency of recovery from the swab or other sampling device. The results obtained must be corrected for the incomplete recoveries due to the sampling and sample preparation processes, and the corrections must be factored into the analytical calculations.

It is also important that the analytical method is sufficiently sensitive to be compatible with the limits established for the residue.

7.4 Specific versus Non-Specific Testing

A non-specific assay may detect a variety of residues, whereas a specific assay may allow any residue other than the single anticipated residue to go undetected analytically. Imagine a bioreactor having many different ingredients including actives, media components, buffers, cleaning agents, solvents, and other components. A specific cleaning assay for the active ingredient may detect only a single contaminant whereas a non-specific assay or test will detect a variety of contaminants.

It is essential to correlate the results from methods used in the cleaning validation studies to the results from other non-specific methods that might be used for routine monitoring of cleaning effectiveness.

Specific test methods generally are required for validation of cleaning for dosage form manufacturing. Non-specific testing methods can be used in the early stages of bulk drug production and for routine monitoring purposes. For example, consider the testing of a cleaning sample with a combination of pH, conductivity, and TOC methods. The pH testing of the sample would detect any residue having acid base character; the conductivity testing would detect any ionic or inorganic material; and the TOC testing would detect any organic residue. Another major advantage of non-specific testing is that these methods are often very easily carried out, are highly sensitive and do not involve major sample preparation.

Table 2 indicates a listing of some of the specific and non-specific testing methods. It is certainly by no means an all-inclusive listing but it should give the reader a general idea of what constitutes a specific or non-specific method.

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Table 2
Specific versus Non-Specific Testing Methods

Specific Test Methods	Non-Specific Test Methods
Near Infrared (NIR) Spectrophotometry	Total Organic Carbon (TOC)
High Performance Liquid Chromatography	pH
Mid Infrared (MIR) Spectrophotometry	Titration
Atomic Absorption	Conductivity
Capillary Electrophoresis	Gravimetric
Enzyme Immunosorbant Assay (ELISA)	

7.5 Analytical Methods

This section addresses the most commonly used means of evaluating cleaned surfaces. Methods utilized for analysis of cleaning samples range from simple to complex. The methods also vary greatly in the manner in which samples must be prepared for analysis and testing. Test methods possess distinct advantages and disadvantages and the method of choice depends on the cleaning situation.

This section is not an all inclusive list of every analytical method which may be used for cleaning evaluations. However, it covers the basic requirements of analytical methods utilized in cleaning programs and addresses the specific aspects of the most popular analytical methods utilized for these purposes. The methods are considered individually in the following section.

7.5.1 Direct Surface Analysis

Various methods can be used for direct surface analysis. Visual examination of equipment is a form of direct surface analysis and was discussed earlier.

In addition to direct visual examination, other methods such as photo electron emission can be used. Utilization of this technique involves placing a probe on the actual surface after first calibrating on a clean surface. The photo electron emission technique is capable of detecting both organic and inorganic contamination.

Advantages:
- quick
- no sample preparation
- non-invasive

Limitations:
- new, non-proven technique
- expensive
- non-specific sample site selection

Research is also continuing to develop techniques for the direct evaluation of surfaces using diffuse reflectance spectroscopy (DRS) and near infrared (NIR). A major advantage of these techniques as well as direct surface analysis is that there will be no necessity to allow for incomplete recovery as in current sampling methodology (i.e., recovery studies).

7.5.2 pH

The measurement of pH can be a valuable, useful and sensitive test for cleaning when residues have acidic or basic properties. Major advantages of this direct method is that no sampling processing is necessary and that readings can be obtained directly by inserting a pH probe into the sample solution. pH probes may be used in-line in various manufacturing equipment and water systems. Since many commercial cleaning agents have strongly acidic or basic character, this simple measurement is an additional piece of evidence that the cleaning agent has been removed following the cleaning procedure.

Advantages:
- rapid, inexpensive
- adaptable to on-line monitoring

Limitations:
- non-specific
- not appropriate for specific validation experiments
- for water soluble materials only

7.5.3 Conductivity

The measurement of conductivity is usually accomplished in a similar fashion to pH measurement, i.e., via a probe unit. Conductivity is strongly sensitive to any ionic or soluble inorganic contaminant present. The technique is extremely sensitive and is also commonly used (in-line) in water systems to monitor the quality of pharmaceutical grade water.

Advantages:
- rapid, inexpensive
- adaptable to on-line monitoring

Limitations:
- non-specific
- not appropriate for specific validation experiments

7.5.4 Total Organic Carbon (TOC)

The TOC method is based on oxidizing the carbon present and measuring the carbon dioxide produced. One way of applying the TOC method to a cleaning validation testing strategy is to assume that all residues detected are due to the most potent or toxic potential contaminant, usually the active ingredient. When calculating the results, the worst case assumption is used and all carbon is back-calculated to the most toxic material. If this calculation gives results which are less than the previously established limits, then it should not be necessary to specifically identify the contaminant since the worst case assumption was made. If results exceed the previously determined limit, then specific analytical methods such as high

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performance liquid chromatography (HPLC) or other appropriate specific methods could be used to determine if the residue was active ingredient, excipient, or cleaning agent.

TOC is potentially applicable to any residue containing significant amounts of carbon; however, it is more useful for detecting medium to large molecular weight compounds than for smaller molecules. The residue must also be soluble in water.

Because of the non-specific nature of TOC, some companies prefer to utilize the method to identify the most difficult to clean locations of the equipment. Other companies use TOC for regular monitoring of the cleaning process once the cleaning validation program is completed.

Advantages:
- broad spectrum
- low level detection
- on-line capability
- rapid turn-around

Limitations:
- non-specific
- aqueous soluble samples only

Special Validation Concerns:
- recovery of sampling technique for specific analytes
- linearity
- detection limit
- precision

7.5.5 Enzymatic (Bioluminescence)

This method is primarily applied to biologicals. It is highly sensitive and reproducible. A special swab is used which carries out the chemistry required prior to insertion of a sample into the instrument. The chemistry is based on the reaction of ATP with luciferin/luciferase to generate bioluminescence which can be quantitated with a simple, portable instrument.

Advantages:
- ultimately specific
- very sensitive

Limitations:
- expensive
- difficult to develop and validate
- may not provide accurate results if proteins are denatured

7.5.6 Light Microscopy

Microscopy is a method of identifying contaminants on equipment and within products. Microscopy has been taken to a new level of sensitivity and identification largely by forensic scientists involved in the investigation of crimes. In many cases, companies have conventional

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light microscopy and scanning electron microscopy (SEM) expertise available within their own basic research units. Another practice which has greatly enhanced the application of microscopy to practical situations has been the combination of light microscopy with other powerful analytical techniques such as x-ray diffraction, mass spectrometry, and nuclear magnetic resonance (NMR). Previously, small amounts of contaminants could be isolated but there was not enough material to characterize or determine the identity of the material. Now, for example by combining SEM and x-ray diffraction it is possible to do a complete elemental analysis of the material and readily identify the contaminant using only very small quantities of material.

One of the practical applications of microscopy is in the evaluation and identification of unknown contaminants on new equipment. New equipment may have been "coated" at the equipment manufacturing site with materials to prevent corrosion; it may have been subjected to various dyes to validate spray ball patterns required for cleaning validation; and it may have been further contaminated by unknown airborne contaminants during transportation from the equipment manufacturer to the pharmaceutical purchaser. The pharmaceutical user of the equipment has no knowledge of what contaminants to look for, analytically.

Advantages:
- provides quick qualitative identification of contaminants
- can complement results from non-specific quantitative techniques such as gravimetric analysis and TOC

Limitations:
- not quantitative
- somewhat subjective

7.5.7 Gravimetric Analysis

Gravimetric analysis can be useful under the proper circumstances. In the case of large equipment, dedicated to the production of a single active ingredient, there may be only a single potential residue. In this case, it may be quite feasible and practical to consider rinsing the entire equipment, evaporating the rinse solvent to dryness and simply weighing the residue.

Advantages:
- broad spectrum
- simple, minimal cost

Limitations:
- non-specific

Special Validation Concerns:
- recovery of sampling technique for specific analytes

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7.5.8 Titration

Titration is another simple analytical method which is often overlooked even though it might provide valuable information in the proper cleaning situation. This method has good potential for application to the analysis of residues of actives as well as cleaning agents.

Advantages:
- moderate specificity, depending upon titration type
- fairly rapid, inexpensive

Limitations:
- moderate sensitivity
- for water soluble materials only

Special Validation Concerns:
- linearity, recovery, specificity, detection limit, precision

7.5.9 High Performance Liquid Chromatography (HPLC)

Generally, HPLC has excellent sensitivity with ultraviolet (UV) detectors. In cases where the residues do not have adequate UV response, other types of detectors, e.g., the evaporative light scattering detector (ELSD) or refractive index detectors, may be useful.

HPLC has the major advantage of being highly specific in nature. Another advantage is that organic solvents may be used for swabbing and may not interfere with the analysis.

HPLC assays are generally automated and highly reproducible. Results can be automatically calculated and printed out with minimal analyst intervention. The retention time of the eluting samples allows the technique to be considered highly specific.

Advantages:
- highly specific
- moderately to highly sensitive
- highly quantitative
- equipment and methods widely available

Limitations:
- longer sample turn-around time
- relatively expensive

Special Validation Concerns:
- recovery, specificity, detection limit

7.5.10 Thin Layer Chromatography (TLC)

Thin Layer Chromatography is a sensitive technique which uses very simple equipment and principles. TLC has been used for the analysis of residues of actives and cleaning agents.

Advantages:
- highly specific

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- moderate-to-high sensitivity
- fairly inexpensive

Limitations:
- moderate-to-high sensitivity
- visual endpoint detection is not quantitative
- automatic readers are semi-quantitative
- lengthy process to perform sample preparation

Special Validation Considerations:
- recovery, specificity, detection limit

7.5.11 Capillary Zone Electrophoresis (CZE)

Also known as capillary electrophoresis (CE), this technique has been applied mostly to the biotechnology industry and is effective for evaluating residues of proteins, amino acids, and certain cleaning agents. The technique is highly specific and quite sensitive. It's disadvantages are that only a single sample can be run at a time, thus a series of samples would require lengthy time periods and that most companies do not have this equipment in their labs requiring additional expenditures. CEZ works best for large bipolar molecules.

Advantages:
- highly specific
- highly quantitative
- sensitive

Limitations:
- expensive

Special Validation Concerns:
- recovery
- specificity
- detection limits

7.5.12 Fourier Transform Infrared (FTIR)

FTIR involves the application of advanced mathematical concepts to multiple infrared scans of a sample. The technique is both qualitative and quantitative. FTIR is suitable for residues of actives as well as cleaning agents and has good sensitivity. It's major drawback is that the equipment is quite expensive and a library of spectra must be developed for comparison purposes.

Advantages:
- specific
- qualitative
- can be quantitative

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Limitations:
- expensive
- requires extensive library of spectra

7.5.13 Enzyme Linked Immunosorbant Assay (ELISA)

An ELISA assay is an antigen-antibody type reaction involving the use of specific chemicals developed especially for the residue involved. It is very specific. ELISA assays typically are used for analysis of protein residues resulting from manufacturing of biotechnology type products. While these assays are very sensitive, they are also costly to develop and validate. It should also be noted that an ELISA method developed for a protein will not detect the same protein once it is denatured. Many proteins are easily denatured by the cleaning process, and the method would fail to detect significant amounts of protein in the denatured form.

Advantages:
- ultimately specific
- very sensitive

Limitations:
- very expensive
- difficult to develop and validate
- labor intensive
- may not provide accurate results if proteins are denatured

7.5.14 Atomic Absorption/Ion Chromatography (AA/IC)

AA/IC is another fairly complex technique which has been applied, although rarely, to analysis of cleaning samples. It has the advantage of being specific and very sensitive, but suffers the disadvantage of involving expensive equipment. AA/IC has a fairly narrow potential area of application in cleaning analysis; however, for the company manufacturing potent ionic or inorganic products it is a potentially useful application. For a company already having this equipment, it could also be readily applied to the analysis of residues of cleaning agents.

Advantages:
- very specific
- sensitive

Limitations:
- generally only useful for metals, salts and metal complexes
- expensive

7.5.15 Ultraviolet (UV) Spectrophotometry

Although UV has been applied to analysis of many products and raw materials, it often does not have the required sensitivity for pharmaceutical products. It is useful for those cases where the residue limits are high enough that an analytical technique of moderate sensitivity will suffice.

Advantages:
- moderately to highly specific
- high sensitivity
- may be used as a screening method or for confirmatory ID

Limitations:
- requires more technical expertise and more expensive equipment than some of the other methods.

Special Validation Concerns:
- recovery, specificity, linearity, detection limit, precision

7.6 Pass-Fail Testing Methods

Pass-fail type testing, also known as "go-no go" testing is used in many analytical situations and has been widely used over the years for detection of impurities in raw materials and products. In actual application to testing, the analyst is looking for a physical change such as a color change or development of a cloudy solution. The difficulty with the development of such tests for cleaning testing is in knowing the actual quantitative level of the transition, i.e., the break point between success and failure. Often the transition point is a range. If this is the case, the range must be known and it's relationship to the limits must be established in the validation process. Another difficulty is in not knowing how close to the transition point your actual sample may be. The actual result, although passing, could have been very close to failure and with normal plus/minus variation it could fail on the next sample.

7.7 Analytical Methods Validation

The analytical methods used for testing cleaning samples must be validated for accuracy, precision, linearity, ruggedness, robustness, sensitivity and recovery. The reader is encouraged to refer to appropriate sources on analytical method validation (e.g., ICH guidelines, etc.).

7.8 Microbial and Endotoxin Detection and Testing

Testing methods used to isolate, quantitate, and speciate bacteria and associated endotoxins for cleaning studies are the same as those used routinely in the microbiology laboratory. Sterile swabs and samples from rinse solutions can be used as vehicles to generate samples for microbial testing. Alert levels and/or action levels should be established. In addition, cleaning agents should be checked to identify their level of bioburden, if any. Refer to the literature for more detail on endotoxin detection methods including gel clot, chromogenic and turbidometric LAL methods or rabbit pyrogen.

Isolated microorganisms should be identified to an appropriate level to determine whether they are of particular concern (pathogens, gram negative, etc.). Special cleaning and depyrogenation methods may be necessary depending on the nature of the bioburden.

8. 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 acceptance criteria should be:

- practical
- verifiable
- achievable
- scientifically sound

The limits should be practical in the sense that the limit chosen should be appropriate for the actual cleaning situation to be validated. Also, the limits must be verifiable by some means of detection. In addition, the limits must be achievable by the analytical methodology available for the specific product. Most importantly, the company should develop a scientifically sound rationale for the limits chosen.

8.1 The Scientific Rationale for Cleaning

It is very important that cleaning limits not be selected arbitrarily but, rather, that there be a logical and scientific basis for the numerical limit selected. The scientific rationale is normally included in the limits section of the protocol for the cleaning validation. The scientific rationale which supports the actual limit should be logical, comprehensive, and easily understood.

8.2 Contamination of the Next Product

Product residue remaining on equipment contaminates a subsequently manufactured product. Thus, it is important to have information about the potential contaminant as well as the product which could become contaminated.

8.3 Considerations for Developing Limits

There are many areas that should be considered prior to establishing cleaning validation limits (see Table 1). Once these areas have been considered, one can establish a risk assessment factor appropriate for use in determining limits.

8.4 Limits Based on Medical or Pharmacological Potency of the Product

One basis of establishing limits is a mathematical calculation which allows a certain fraction of the therapeutic dose to carry over into each dosage unit of the following product.

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Safety Factor

Approach	Approach Typically Applicable To
1/10th to 1/100th of a normal daily dose	topical products
1/100th to 1/1000th of a normal daily dose	oral products
1/1000th to 1/10,000th of a normal daily dose	injections, ophthalmic products
1/10,000th 1/100,000th of a normal daily dose	research, investigational products

Possible approaches to safety factor determination are discussed in Sections 8.5 and 8.6, below. Tthe fraction of dose reduction is a measure of the risk involved and should be assessed by the company depending on the actual manufacturing situation.

8.5 The Basis for Quantitative Limits

Actual numerical limits are usually based on one of the following:

- the medical or pharmacological potency of the product
- the toxicity of the residue
- the analytical limit of detection

Different manufacturing and cleaning situations may require different approaches and each approach will be discussed individually. It is also important to factor the following product to be manufactured in the same equipment into the limit calculation. Factors such as the batch size of the following product, the route of administration, and the largest daily dose of subsequent product which might be administered are important in the calculation.

All of these factors mentioned previously are usually summarized in an equation which may take the following general form:

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

where: MAC = the maximum allowable carryover
TD = a single therapeutic dose
BS = the batch size of the next product to be manufactured in the same equipment
SF = the safety factor
LDD = the largest daily dose of the next product to be manufactured in the same equipment

This mathematical equation shows that the batch size of the next product as well as the largest daily dose of the next product are required for the calculation. If the next product to be manufactured is not known, then the smallest batch size of any product manufactured previously in the equipment can be used. When a new worst case is to be manufactured in the equipment, then this would be

evaluated by the change control process and new limits could be imposed on the cleaning for the equipment.

As an example of the calculation of an overall limit, consider the case of a product A having a single therapeutic dose of 100 mg. Assume that the product is given by the oral route of administration. Let's also assume that the next product to be manufactured in the same equipment has a batch size of 10 Kg, and a largest daily dose of 800 mg. Use a safety factor (SF) of 1/1000. In this case, the calculation would be:

$$MAC = \frac{TD \times BS \times SF}{LDD} = \frac{100mg \times 10{,}000{,}000mg \times 1/1000}{800mg} = 1250mg$$

This is the total limit for all residues on all equipment used to manufacture the product.

8.6 Limits Based on the Toxicity of the Residue

Using the therapeutic dose as the basis of limits calculations is appropriate for situations where the material is an active ingredient and therapeutic dosage levels are known. There are other situations, however, where the material is not medically used and there are no known therapeutic dose data available. Examples are precursors and intermediates used in chemical synthesis (i.e., manufacture of active pharmaceutical ingredient (APIs)), and cleaning agents. These materials have no quantitative therapeutic dosage levels. Yet, they may have a medical or toxic effect in the body. In these cases, it is necessary to base the limits calculations on the toxicity of the material.

This can be done by using the method described above for pharmacological activity with substitution of the toxic dose. Alternatively, where toxicity is expressed as LD_{50}, the following methodology can be used.

$$NOEL = LD_{50} \text{ x emperical factor}$$

$$ADI = NOEL \times AAW \times SF$$

where: NOEL = no observed effect level
LD_{50} = lethal dose for 50% of animal population in study
empirical factor = derived from animal model developed by Layton, et.al.
ADI = acceptable daily intake
AAW = average adult weight
SF = a safety factor

This equation can be applied to a pharmaceutical cleaning validation study for the purpose of calculating a limit. The result would be as follows:

$$MAC = \frac{ADI \times B}{R}$$

where: MAC = maximum allowable carryover
B = smallest batch size of any subsequent product
R = largest daily dose of any product made in the same equipment

The only changes made to the equation are those representing the batch size and the largest daily dose of the subsequent product. The basic value of this approach is, as indicated previously, that a limit can be calculated for cleaning validation purposes based solely on the toxicity of the material. It is important that the LD_{50} be from the same route of administration as the product for which the limit is calculated. For example, if the product is an oral product, then the LD_{50} should be from the oral route of administration. Likewise, if the product is an intravenous injection, then the LD_{50} should also be by the intravenous route of administration.

8.7 Limits Based on the Analytical Limitations

These approaches to establishing limits are based on the cleaning limit being the limit of analytical detectability. In some cases, where the danger of contamination and the consequences are of a critical nature, this may be a viable approach. However, in the great majority of cleaning situations, this extreme degree of cleaning is neither necessary nor justified. When carried to extremes the cost of cleaning can easily surpass the cost of the product. The key to selecting this approach is the nature of the product (i.e., its toxicity and stability) and the nature and use of other products made in the same equipment. A further problem with using these approaches is that constant advances in analytical technology means that more sensitive analytical procedures are constantly being developed.

8.8 The Meaning of "None Detected"

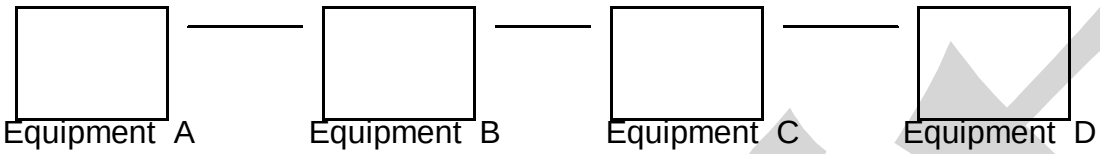
The use of the term "none detected" is very common in the laboratory. It is important to correctly interpret the meaning of this term, especially where cleaning samples are involved. "None detected" does not equal zero, i.e., it does not mean there was no residue present. All that can be stated about such results is that the level of residue was below the detection capability of the analytical technique or instrument, often referred to as the sensitivity of the method. The sensitivity parameter is one of the most important parameters of an analytical method and sensitivity must be validated as a part of the analytical methods validation.

The sensitivity of an analytical method is often expressed as either the limit of detection or the limit of quantitation. The sensitivity of the analytical method may be used to establish the actual cleaning limits. In cases where the cleaning validation study results in "none detected" the sensitivity of the analytical method could be used to calculate the maximum amount of residue which could be present.

8.9 Dividing a Limit Among Various Pieces of Equipment

In order to evaluate a processing operation composed of several unit operations, it is important to consider the accumulated residue from each piece of process equipment. This is the sum of all

residues which were present on the various pieces of manufacturing and packaging equipment. The total residue is equal to the sum of all residues in the manufacturing "train" as represented in the following diagram:



Equipment A could be, for example, a powder blender; equipment B could be a granulator; equipment C could be a compressing machine; and equipment D might represent a packaging filler for a solid dosage form such as a tablet. For a liquid product, equipment A could be a mixing tank; equipment B could be a holding tank; equipment C could be transfer piping to the packaging department; and equipment D might be the liquid filling equipment.

In many manufacturing operations each piece of equipment is a discrete unit. Since the equipment pieces are usually separate stand-alone units, it is necessary to determine limits for each individual equipment piece.

An equipment train should be delineated to separate those portions in which the residue would be evenly distributed (e.g., blender, granulator) from those in which the residue could be transferred to an individual dosage unit (e.g., tablet press, encapsulating machine, tablet filler).

Prior to the dose forming step the allowable residue may be distributed across the equipment. The dose forming step (compression, filling) must use a different, tighter limit to restrict potential carryover to a single product dose.

9. Ongoing Verification of Cleaning

9.1 Verification of Cleaning

Verification of cleaning involves the performance of testing which confirms that the cleaning method is adequately removing substances to established levels. The CGMP regulations require inspection of each piece of equipment immediately before use to ensure its cleanliness. However, additional verification may be necessary depending on the complexity of the equipment.

9.2 Monitoring of Automatic and Manual Cleaning

For automatic cleaning methods, ongoing verification may not be required. If the automated system is designed, installed and validated appropriately and the process reproducibility is confirmed, no further verification should be necessary. For semi-automated processes, a determination must be made about the predicted reproducibility of the process over time.

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Manual cleaning generally requires periodic verification. Verification should confirm the ongoing appropriateness of the training program as well as the operator's ability to perform the cleaning process.

One way in which corporations provide for the ability to perform ongoing or occasional verification is to correlate rinse results to other residual data. Once this data is collected, it is possible to confirm that the residual levels meet the predetermined requirements. It may be used as an adjunct to cleaning validation or in a clinical supply setting where consistency of cleaning may not have been established.

10. Change Control

All aspects of cleaning should fall under the auspices of a change control policy. Cleaning standard operating procedures, assay methods, equipment, detergents, product formulations, batching methods and the like should all be documented at the time of the validation effort. Changes to these items will require formal documentation and approval. Typically, corporate change control policies are in existence which will govern the review and approval of these changes.

If a firm chooses not to pursue the verification of cleaning on a periodic or occasional basis, changes performed under the change control program will require reconfirmation of the cleaning validation results, or verification. If the change is deemed to be fundamental to either the grouping philosophy on which the validation was founded, or to the cleaning method, the change may require revalidation.

Revalidation, in contrast to verification, may require that portions of the initial cleaning validation program be repeated. Revalidation may differ from verification only by the amount or type of sampling that is performed. Typically the sampling and testing that are performed during revalidation are more stringent than that performed during routine or occasional monitoring. Revalidation of cleaning may incorporate aspects of both validation and verification, but in accordance with a firm's internal policies may be restricted to one or the other.

The careful planning and execution of the revalidation program will allow for compliance in the ongoing operations of the facility.

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11. Appendices

11.1 Glossary of Terms

acceptable daily intake	an amount of a substance administered or consumed on a daily basis that will not produce a pharmacological or toxic response
analyte	substance for which an analysis is being performed
API	active pharmaceutical ingredient
automated cleaning	a cleaning procedure which relies on a sequence of programmed, reproducible steps (usually via mechanical and/or electronic devices)
batch production	a series of unit operations performed according to a single manufacturing order during the same cycle of manufacture to produce a specific quantity of a drug having uniform character and quality within specified limits
blank	analytical method control sample used to establish a baseline for the result, e.g., as in a titration where one or two drops of the titrant must be added to the blank to cause an indicator color change
bulk pharmaceutical	generally known as bulk pharmaceutical chemicals; also called primary pharmaceuticals or active pharmaceutical ingredients
campaign	processing of more than one product in the same facility and/or equipment in a sequential manner; only one product is present in any one manufacturing area of the facility at a time
CGMP	Current Good Manufacturing Practices
change control	a documented system for reviewing proposed or actual changes that might affect a validated system or process; change control includes the determination of any corrective action required to ensure that the system remains in a validated state
change-over	actions required for switching multi-product equipment and facilities from one product to another
clean (*v.*)	the implementation of procedures to render a piece of equipment, or a system, free of adulterants and contaminants

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clean(liness) (*adj.*)	visually clean - absence of materials which would adulterate a product when inspected with the eyes detectably clean - absence of materials which would adulterate a product down to the level of detection chemically clean - absence of all chemicals which would adulterate a product
clean-in-place (CIP)	cleaning without the need to disassemble equipment (may be either automatic or manual)
CIP system	a system, usually automatic, used to clean equipment in place
clean-out-of-place (COP)	the cleaning performed, usually manually, after disassembly of equipment or a system
COP system	a system which may be automatic, semi-automatic or manual, used to clean equipment out of place, e.g., a parts washer
cleaning agent	usually a detergent or surfactant that reduces the surface tension of a solvent to increase its effectiveness
cleaning validation	demonstrating that cleaning results are consistent and reproducible, usually by sampling critical and representative sites on the equipment after cleaning
contaminant	extraneous substance that exists in a product
continuous process	a series of operations performed according to a manufacturing order so as to provide a steady stream of a drug having uniform character and quality within specified limits
control parameters	those operating variables that can be assigned values that are used to regulate a process
coverage	the exposure of equipment surface area to the cleaning process
critical site	area of a piece of equipment on which residual materials are trapped or concentrated (e.g., because of location, surface or equipment design) and which is likely to contribute all of the contamination to a single dose (i.e., "hot spot")
dead leg	a pipe with restricted flow or agitation exceeding the length of six pipe diameters

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dedicated equipment	equipment that is to be utilized for a single product or product family
degradation	breakdown of material during manufacture or after exposure to the cleaning process
depyrogenation	removal or destruction of pyrogens
detergent	a synthetic wetting agent and emulsifier that can be added to a solvent to improve its cleaning efficiency
disinfection	to adequately treat equipment, containers, or utensils by a process that is effective in destroying vegetative cells of microorganisms of public health significance, and in substantially reducing numbers of other undesirable microorganisms
endotoxin	lipopolysaccharide, usually from gram negative bacteria
equipment grouping	equipment closely related by design, as to be considered the same for the purposes of cleaning
equipment train	the sequence of equipment through which a product is produced or processed
final rinse	the last rinse of a piece of equipment during the cleaning procedure (see rinse)
hot spot	see critical site
impingement	to cause to strike
impurity	any extraneous substance or contaminant present in the drug substance or drug product
LD_{50}	the dose resulting in a fifty percent mortality of the test animal
largest daily dose	maximum daily dose of the next product to be produced in the equipment train
limit	a prescribed maximum and/or minimum tolerance
limit of detection	the lowest concentration of analyte in a sample that can be detected, but not necessarily quantitated, under the stated experimental conditions

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limit of quantitation	the lowest concentration of analyte in a sample that can be determined with acceptable precision and accuracy under the stated experimental conditions
major equipment	any process equipment which is uniquely identified within the drug product batch record (e.g., autoclave, batch tank, blender, encapsulator, filler, tablet press)
manual cleaning	a cleaning procedure requiring operator performed critical steps (e.g., scrubbing with a brush or rinsing with a hose)
maximum allowable carryover	the maximum amount of carryover from one product to the next that will not produce a therapeutic dose, corrected for a safety factor (e.g., 1/1000)
minimum pharmacological dose	the minimum dose required to elicit a response in vitro or in vivo
minimum therapeutic dose	the minimum dose that will produce a pharmacological response as derived by medical criteria
minor equipment	ancillary equipment (e.g., dispensing containers, utensils, scoops) associated with a drug product manufacturing process
peptizing	to bring into colloidal solution, esp. proteins
placebo	inert material or formulation
placebo scrubbing (or solid washing)	use of an inert material to mechanically displace and dilute residuals
process validation	establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes
product family	a group of closely formulated products with the same active ingredient(s)
prospective	establishing documented evidence that a system validation does what it is supposed to do, based on information generated before actual implementation of the process
protocol	a document with agreed upon set of standards and tests

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prototyping	use of a representative drug product and/or piece of equipment to demonstrate a cleaning procedure can achieve adequate levels of cleanliness for similar product and/or equipment families
pyrogen	a material which elicits a pyrogenic response (fever)
rinse (aqueous/non-aqueous)	to cleanse or treat an equipment as part of a cleaning procedure
safety factor	a predetermined value (e.g., 1/1000) used to minimize the uncertainty of a calculated limit
sanitize	to make physically clean and to remove and destroy, to the maximum degree that is practical, agents injurious to health
semi-automated	a system controlled partly by mechanical/electronic devices, but requiring some manual intervention
serial cleaning	cleaning performed in the midst of a production campaign; serial cleaning is usually less intensive than the procedure used between different products
swab	an absorptive device used to remove a sample from a surface
therapeutic dose	an amount of drug that will produce a pharmacological response
threshold dose	see "no-effect"
toxic dose	the minimum dose required to produce a harmful, poisonous effect
visually clean	absence of visible contaminants
worst case	the highest or lowest value of a given control parameter, maximum system load, or maximum or minimum environmental conditions actually evaluated in a validation exercise

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11.2 Suggested Reading

Journal Articles

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J.V. Rodricks, "Risk Assessment and Animal Drug Residues," Drug Metabolism Review, Vol.22, No N6-8, p. 601, 1990.

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A.M. Thayer, "Bioremediation - Innovative Technology for Cleaning Up Hazardous Waste," Chemical & Engineering News, August 1991.

N.J. Yess, "Residues in Food," J. Assoc. Off. Analytical Chemistry, Vol. 73, No. 5, 1991.

Guidelines

FDA CGMP

USP

OSHA Industrial Hygiene Manual

NIOSH Industrial Hygiene Manual

Mid-Atlantic Regional Drug Inspection Program, Inspection Guidance for Prescription Drug Plants, 1990

ICH Analytical Methods Validation

Conference Summaries/Books/Unpublished Articles

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