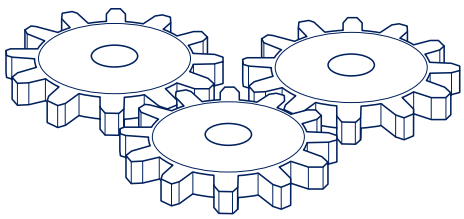
Technical Report No. 29 (Revised 2012)

Points to Consider for Cleaning Validation

PCMO[SM]

Paradigm Change in Manufacturing Operations[SM]

2012



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PDA Task Force on Technical Report No. 29 (Revised 2012): Points to Consider for Cleaning Validation

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Points to Consider for Cleaning Validation

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ISBN: 978-0-939459-48-3

Paradigm Change in Manufacturing Operations (PCMO[SM])

PDA launched the project activities related to the PCMO program in December 2008 to help implement the scientific application of the ICH Q8, Q9 and Q10 series. The PDA Board of Directors approved this program in cooperation with the Regulatory Affairs and Quality Advisory Board, and the Biotechnology Advisory Board and Science Advisory Board of PDA.

Although there are a number of acceptable pathways to address this concept, the PCMO program follows and covers the drug product lifecycle, employing the strategic theme of process robustness within the framework of the manufacturing operations. This project focuses on Pharmaceutical Quality Systems as an enabler of Quality Risk Management and Knowledge Management.

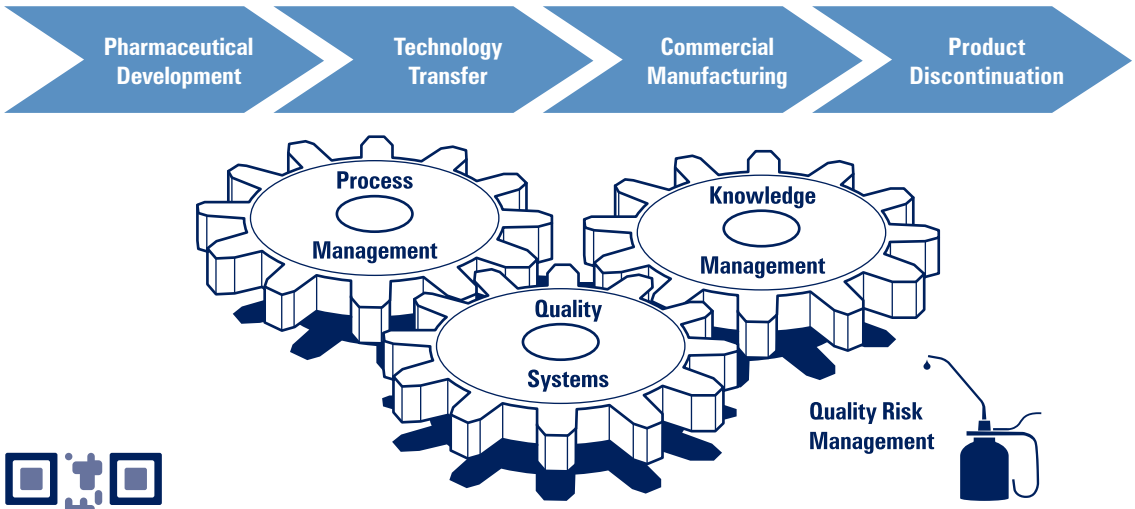
Using the Parenteral Drug Association's (PDA) membership expertise, the goal of the Paradigm Change in Manufacturing Operations Project is to drive the establishment of 'best practice' documents and /or training events in order to assist pharmaceutical manufacturers of Investigational Medicinal Products (IMPs) and commercial products in implementing the ICH guidelines on Pharmaceutical Development (ICH Q8, Q11), Quality Risk Management (ICH Q9) and Pharmaceutical Quality Systems (ICH Q10).

The PCMO program facilitates communication among the experts from industry, university and regulators as well as experts from the respective ICH Expert Working Groups and Implementation Working Group. PCMO task force members also contribute to PDA conferences and workshops on the subject.

PCMO follows the product lifecycle concept and has the following strategic intent:

- Enable an innovative environment for continual improvement of products and systems
- Integrate science and technology into manufacturing practice
- Enhance manufacturing process robustness, risk based decision making and knowledge management
- Foster communication among industry and regulatory authorities

The Product Life Cycle



For more information, including the PCMO Dossier, and to get involved, go to www.pda.org/pcmo

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1.0 Introduction

Cleaning validation plays an important role in reducing the possibility of product contamination from pharmaceutical manufacturing equipment. It demonstrates that the cleaning process adequately and consistently removes product residues, process residues and environmental contaminants from the manufacturing equipment/system, so that this equipment/system can be safely used for the manufacture of specified subsequent products (which may be the same or a different product). As used in this Technical Report, "product" may be a drug product, active pharmaceutical ingredient, intermediate, or another type of formulation. If "drug product" is intended, that terminology will be utilized. Principles and practices given in this report may apply to a variety of manufacturing situations. It is incumbent on the reader to decide the appropriateness of those principles and practices to his/her specific situation.

This report builds on the 1998 *PDA Technical Report No. 29, Points to Consider for Cleaning Validation* ***(1)***. This report also has utilized principles and specific wording from the 2010 *PDA Technical Report No. 49, Points to Consider for Biotechnology Cleaning Validation* ***(2)***. The authors of this revised Technical Report #29 would like to thank the members of the Task Forces who were responsible for those two earlier documents for making our job easier.

This revised Technical Report presents updated information that is aligned with lifecycle approaches to validation and the International Conference on Harmonisation (ICH) guidelines Q8 (R2) - *Pharmaceutical Development,* Q9 - *Quality Risk Management* and Q10 - *Pharmaceutical Quality System* ***(3,4,5)***. Also, this report aims to assist readers who want to create or benchmark a cleaning validation program for their equipment and facilities.

This Task Force was composed of European and North American professionals from pharmaceutical manufacturers, cleaning chemical suppliers, and consulting companies. The report has undergone a global, technical peer review to ensure concepts, terminology, and practices presented are reflective of sound science and can be used globally.

1.1 Purpose/Scope

This Technical Report covers all facets of cleaning validation for pharmaceutical manufacturers, including both manufacturers of APIs and drug products. It also applies to biotechnology manufacturing; however, the reader should consult *PDA Technical Report No. 49, Points to Consider for Biotechnology Cleaning Validation* for more detail and specifics for biotechnology manufacturing ***(2)***. We have included a lifecycle cleaning validation approach, including design/development of the cleaning process, process qualification (including the protocol runs), and ongoing validation maintenance. While the document discusses risk-based approaches, it does not provide details about risk-based manufacturing. PDA has formed a Task Force to write a Technical Report on that topic.

We cannot emphasize enough how important risk analyses are in the selection of and validation of cleaning processes and their validation. This includes the traditional risk analysis based on effects on product quality and on patients. It also includes business risk considerations, such as steps taken to minimize lost product from contamination (even if detection systems are in place to prevent release of that contaminated product for consumer use).

These practices and the associated guidance in this Technical Report are based on technical considerations and should be applicable in all regulatory environments. However, the intent of this Technical Report is not to provide a detailed plan or roadmap for a pharmaceutical manufacturer to perform cleaning validation. Rather, as the title suggests, it presents "points to consider" as one designs a cleaning validation program for process equipment based on an understanding of one's manufacturing and cleaning processes. In cleaning validation, there are generally *multiple* ways to accomplish the

same goal of a compliant, scientifically sound and practical cleaning validation program. Where options are given, the rationales for such options are also generally given. Examples are not meant to be prescriptive or limiting; they merely illustrate a certain practice. Actual acceptable practices should not be considered limited by the discussion in this Technical Report. Based on an understanding of the unique nature of any individual situation, different approaches or additional issues should also be considered. Sound science based on an understanding of the cleaning and manufacturing processes may lead to other equally acceptable practices. The Task Force that developed this document hopes that the report will be used in this spirit and will not be solely used as a checklist.

This report should be considered to be a resource to help guide the development or evaluation of a cleaning validation program. It is not intended to establish mandatory standards for cleaning validation. It is intended to be a single-source overview for pharmaceutical manufacturers that complements existing regulatory guidance and other documents referenced in this document. The reader should also be aware that a specific topic may be discussed in several sections of this Technical Report. Therefore, a more complete perspective may be obtained by considering all relevant sections about a certain topic. Furthermore, while many approaches are presented here, specific approaches utilized for a given cleaning process should be selected based on a good understanding of that process, as well as the appropriateness of the selected practice for that specific situation. It is not enough to merely say that the practice is mentioned as an acceptable one in PDA Technical Report No. 29; each firm should be prepared to defend why the selected approach is a valid one for its operations ***(1)***.

2.0 Glossary of Terms

Acceptable Daily Exposure
A dose that is unlikely to cause an adverse effect if an individual is exposed, by any route, at or below this dose every day for a lifetime.

Acceptable Daily Intake
An amount of a substance consumed on a daily basis that is considered at a safe level.

Acceptance Criteria
Numerical limits, ranges, or other suitable measures for the acceptance of test results.

Acceptance Limit
The maximum amount of residue allowed in a product, in an analytical sample, or as an amount per surface area.

Active Pharmaceutical Ingredient (API) or Drug Substance
Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and when used in the production of a drug, becomes an active ingredient of the drug product (also called "drug substance").

Analyte
Substance (usually a residue) for which an analysis is being performed.

Blank
Analytical sample taken to establish background value for the analytical measurement which may be subtracted from an experimental value to determine the "true" value.

Campaign
Processing of multiple lots or batches of the same product serially in the same equipment.

Changeover
The steps taken for switching multiproduct equipment from the manufacture of one product to the manufacture of a different product.

Clean
Having product residues, process residues, and environmental contaminants removed to an acceptable level.

Clean Hold Time
The time from the end of the cleaning process until the equipment is used again (which may be product manufacture, autoclaving, or a steam in place (SIP) cycle).

Cleaning Agent
The solution or solvent used in the washing step of a cleaning process. Examples of cleaning agents are water, organic solvent, commodity chemical diluted in water, and formulated detergent diluted in water.

Cleaning Procedure
The documentation that assures any product and process-related material introduced into equipment as part of the manufacturing process stream is removed and the equipment is adequately stored.

Cleaning Process
A process that is used to remove any product, process-related material and environmental contaminant introduced into equipment as part of the manufacturing stream.

Cleaning Validation
Documented evidence with a high degree of assurance that a cleaning process will result in products meeting their predetermined quality attributes throughout its life cycle.

Cleaning Verification
A one-time sampling and testing to ensure that specified equipment has been properly cleaned following a specific cleaning event.

Contamination
An undesired residue or residue level on cleaned equipment surfaces or in a manufactured product.

Coupon
A small, generally flat portion of a defined material of construction (such as stainless steel or PTFE) and of a defined surface finish, typically used for laboratory cleaning evaluations and/or for laboratory sampling recovery studies

Dedicated Equipment
Equipment used exclusively for the manufacture of only one drug product, bulk drug substance, or intermediate.

Degradation
Breakdown (usually chemical) of material during manufacture (including during and after the cleaning process).

Dirty Hold Time
The time from the end of product manufacturing until the beginning of the cleaning process (also called "soiled hold time").

Dry Equipment
No visible water in the equipment or line when viewed under appropriate lighting conditions.

Equipment Train
The sequence of equipment through which a product is produced or processed.

Free Drained Equipment
No visible water pool in the equipment or line when viewed under appropriate lighting conditions (but may contain water droplets).

Grouping Strategy
A strategy for establishing similar cleaning processes, usually based on similar products or similar equipment, and to validate the cleaning process based primarily on validation data for a representative of the group.

Highly Hazardous Drug Active
A drug active that can cause serious adverse effects at typical doses. Those adverse effects are generally not related to the main therapeutic activity of the drug, and includes effects such as carcinogenicity, mutagenicity, genotoxicity, reproductive hazards, allergenicity, and cytotoxicity.

Investigational Medicinal Product
A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial.

LD_{50}
The dose of a material which results in 50% mortality in an animal test

Limit
A value for a residue above which a cleaning process would not be acceptable.

Marker
Component of a product or a cleaning agent used as an analyte to quantitate the total amount of product or cleaning agent present.

Mock Soil
A soil which is used in place of the manufactured product during a cleaning validation protocol (also called a "surrogate" soil).

Mock Soiling
A process of soiling the equipment for a cleaning validation protocol in which soil is applied to the equipment surfaces to simulate the condition of the soil on those surfaces following typical product manufacturing.

Normal Dose
The therapeutic dose of a product as given on the approved product labeling.

Product Changeover
Procedural steps taken for switching from the manufacturing of one product to another product.

Recovery Study
A laboratory study combining the sampling method and analytical method to determine the quantitative recovery of a specific residue for a defined surface.

Residue
Chemical or microbiological material remaining on equipment surfaces after a cleaning process.

Soil
The chemical or microbiological materials left on process equipment after completion of process manufacturing, but before initiation of the cleaning process.

Worst-Case Process Condition
A condition or set of conditions encompassing upper and/or lower processing limits and circumstances, within standard operating procedures, which pose the greatest chance of product or process failure when compared to ideal conditions (such conditions do not necessarily induce product or process failure).

Worst Case Soil
A soil that is the most difficult to clean from production equipment based on knowledge generated from laboratory studies, scientific properties, and/or production experience.

2.1 Definition of Acronyms

AA: Atomic Absorption

ADE: Acceptable Daily Exposure

ADI: Acceptable Daily Intake

API: Active Pharmaceutical Ingredient

CAPA: Corrective and Preventive Actions

CBER: Centers For Biological Evaluation and Research

CDER: Centers for Drug Evaluation and Research

CFU: Colony Forming Unit

CGMPs: Current Good Manufacturing Practices

CIP: Clean-In-Place

COP: Clean Out-of-Place

CPP: Critical Process Parameters

CQA: Critical Quality Attributes

CZE: Capillary Zone Electrophoresis

DOE: Design of Experiments

ELISA: Enzyme Linked Immunosorbant Assay

EPDM: Ethylene Propylene Diene Monomer Rubber

EU: Endotoxin Units

U.S. FDA: Food and Drug Administration

FMEA: Failure Mode and Effects Analysis

FTIR: Fourier Transform InfraRed

HPLC: High Performance Liquid Chromatography

ICH: International Conference on Harmonisation

ICP: Inductively Coupled Plasma

IMS: Ion Mobility Spectrometry

LOD: Limit of Detection

LOQ: Limit of Quantitation

MAC (or MACO): Maximum Allowable Carryover

NOEL: No Observable Effect Level

NOAEL: No Observable Adverse Effect Level

NIR: Near Infrared

LD_{50}: Lethal Dose 50 Percent

PAI: Pre-Approval Inspection

PAT: Process Analytical Technology

PIC/S: Pharmaceutical Inspection Cooperation Scheme

PLC: Programmable Logic Controller

PPQ: Process Performance Qualification

PTFE: PolyTetraFluoroEthylene

PW: Purified water

QA: Quality Assurance

QbD: Quality by Design

QC: Quality Control

OIT: Operator Interface Terminal

RSD: Relative Standard Deviation

SAL: Surface Acceptance Limit

SEM: Scanning Electron Microscopy

SIP: Steam-In-Place (or Sterilization-In-Place)

SPC: Statistical Process Control

SOP: Standard Operating Procedure

SUPAC: Scale Up and Post Approval Changes

TACT: Time, Action, Concentration and Temperature

TLC: Thin Layer Chromatography

TNTC: Too Numerous To Count

TOC: Total Organic Carbon

TTC: Threshold of Toxicological Concern

UPLC: UltraPerformance Liquid Chromatography

UV/Vis: Ultraviolet/visible Spectrophotometry

WFI: Water for Injection

WHO: World Health Organization

3.0 Cleaning Process Design and Development

This section describes the application of operational parameters and measurements, design of laboratory scale experiments, selection of appropriate test soils, and scale-up for the cleaning of the manufacturing equipment. Additionally, the concept of "Design Space," a Quality by Design approach to the development of pharmaceutical processes, is discussed and applied to the development of cleaning processes.

The cleaning process requires design and development *prior to* implementation in a manufacturing plant to ensure the cleaning process and equipment are acceptable for use.

The operational parameters that describe the cleaning process include:

- Cleaning agent
- Concentration
- Contact time
- Cemperature

Factors which affect the cleaning process include:

- Product characteristics
- Product condition

Relevant specifics about the cleaning equipment include:

- Automated cleaning pathways
- The sequence of manual or automated cleaning steps
- Flow rates during each step

These operational parameters should be determined prior to implementation.

Generally, establishment of acceptable cleaning processes (or confirmation of acceptable processes for new soils being introduced to the manufacturing plant) follows a standard progression of activities, beginning with identification of control variables, cleaning measurements, and performance criteria. Laboratory (scale-down) experimentation, analogous to laboratory experimentation for process characterization, along with specific equipment requirements may provide data to establish cleaning parameter control ranges.

3.1 Cleaning Process Design

Design starts with a consideration of the Critical Process Parameters (CPPs) and Critical Quality Attributes (CQAs) of the cleaning system. **Table 3.1-1** lists representative CPPs and CQAs that might be applicable to a cleaning process.

Table 3.1-1 CPP and CQA Considerations that have Potential Risk Impact to a Cleaning Process ***(2)***

Critical Process Parameters	Critical Quality Attributes
• Process temperature	• Visual detection or limits
• Process pressure	• Cleaning agent residues
• Process flow	• Product residues
• Process time	• Microbiological residue limits
• Cleaning agent concentration	• Drainability/drying
• Dirty hold time (soil condition)	• Conductivity/resistivity
• Clean hold conditions	

Table 3.1-2 describes the factors in the cleaning spectrum. For each factor, there is a range of possible operating differences utilized within the industry. The development of a specific process should consider the number and complexity of issues surrounding the cleaning process and the variety of facilities, products and equipment in use.

The cleaning spectrum helps manufacturers to establish the factors which are critical for individual processes, thereby enabling them to set priorities, develop grouping philosophies and establish the ''scientific rationales'' that will govern the cleaning program. The cleaning spectrum can be used during the initial phases of defining a cleaning validation program or during a new product cleaning process development.

The cleaning spectrum includes cleaning program criteria, equipment characteristics, quality attributes of equipment design, formulation/product attributes, and manufacturing/process attributes. All of the factors in the cleaning spectrum directly affect the ability to clean; however, their relative importance and criticality may be different in different situations.

Table 3.1-2 The Cleaning Spectrum

Automated Cleaning	Manual Cleaning
In-place Cleaning	Out-of-Place Cleaning
Dedicated Equipment	Non-Dedicated Equipment
Indirect Product Contact Surfaces	Product Contact Surfaces
Low Risk Site	High Risk Site
Minor Equipment	Major Equipment
Low Risk Drugs	High Risk Drugs
Highly Characterized	Poorly Characterized
Liquid Formulations	Solid Formulations
Easy to Clean Product	Difficult to Clean Product
Materials with a Smooth, Non-porous Surface	Porous Materials
Single Product Facility	Multiple Product Facility
Non-Campaigned Production	Campaigned Production

3.2 Cleaning Process Overview

Cleaning processes generally contain multiple steps. Each step in the process has a function and a set of parameters that are controlled within defined ranges to ensure effective soil (and cleaning agent) removal. Steps in a typical cleaning cycle for a cleaning process are outlined below in **Table 3.2-1**. Details of the cleaning processes may vary from site-to-site and for different types of process equipment. Differences may include the use and type of detergents and/or solvent, presence of an acid cleaning step, concentration of cleaning agents, contact time of cleaning agents on equipment, feed pressure or flow rate, cleaning temperature, and required length or volume, length and/or number of rinse steps.

Table 3.2-1 Cleaning Process Steps (Examples)

Step	Function	Comments
Vacuum or Pre-Rinse	Removal of readily soluble and/or non-adhering residues	Reduction of soil load prior to washing step.
Wash with Cleaning Solution	Removal of soluble and dried residues, solubilization of soils by degradation, heat, and/or wetting with detergents	Primary step for soil and bioburden removal. Often performed at elevated temperatures. May include alkaline detergents or alkali hydroxides, acid detergents or acids, combinations of the two, or may be a solvent or solvent mixture.
Rinse	Removal of suspended or solubilized soils and, if applicable, of cleaning solution	May include a series of pulse rinses, and may include final rinse with higher grade of rinse solvent.
Dry	Removal of water and other solvents	May be done by air or nitrogen flow or by heat. Water removal may be assisted by an organic solvent final rinse.

3.2.1 Physical-chemical Aspects

There are four principal cleaning input parameters that can be varied for each step in the cleaning process. These four parameters are typically referred to as TACT (**T**ime, **A**ction, **C**oncentration, and **T**emperature). These four variables are interrelated and have a direct relationship on the success of each phase in the cleaning cycle. For example, cleaning agents may be heated to increase their effectiveness. The effect of each of these variables on soil removal should be determined and acceptable ranges established as part of the cleaning development effort. (Soil type and condition is an additional input that is discussed in **Section 3.3.3.**)

Time is defined as the length of time for the cycle step. There are two typical ways, direct and indirect, of defining and measuring contact time during a cycle step. Using the direct method, a cycle step counter is used to measure the cycle step time. Time also may be measured indirectly. For example, for a rinse step, volume is sometimes tracked instead of time because the volume and flow rate define a time. For final water rinse, it is also common to add more requirements, such as achieving a specified conductivity level.

Action is the mechanism used to deliver the cleaning agent. This mechanism may be characterized as soak, scrubbing, impingement or turbulent flow. Agitation often enhances the chemical actions of the cleaning agents and helps to increase the effectiveness of the cleaning process, such as by shortening the required contact time. Manual cleaning typically includes soaking or scrubbing as the action to achieve cleaning. Automated cycles typically employ impingement and/or turbulence as a cleaning action. The mechanisms of action should be understood for each cleaning process step. If critical, the flow rate of the cleaning and rinse fluids traveling through the equipment should be specified and verified in the cleaning process. Spray devices have minimum and maximum flow rate requirements, and piping should be flushed at a velocity sufficient to assure adequate coverage and turbulence.

Cleaning agent *concentrations* directly affect the performance of the cleaning process. Selection of

the cleaning agent should consider various aspects including soil type, ease of removal, and need for chelating agents. Cleaning chemicals are available in concentrated forms that are diluted and used in cleaning cycles. Effectiveness of the cleaners may be related to their concentration. Too low of a concentration may result in failure to remove the soil from equipment; too high of a concentration may result in difficulty in removal of cleaning agent residues and may require excessive rinsing. Chemicals may be costly, both in their purchase and disposal, and thus determining the correct concentration of cleaning agent required to ensure cleanability should be considered. The automated dilution and addition of the cleaning agent to the cleaning equipment system must be designed for reproducibility. Regardless of the method of addition, confirmation or verification of the cleaning agent concentration helps verify consistency. For automated cleaning processes, the easiest means to verify cleaning agent concentration for highly alkaline or acidic aqueous cleaning agents is by conductivity. Other considerations in the use of cleaning agents include a toxicity/safety evaluation and the possible need for surfactants, chelants and other functional aids in formulated detergents.

A process should be in place to detect anomalies in detergent concentration based on the mechanism by which chemical make-up is performed. For example, some systems control chemical addition by volume and use conductivity as a confirmation. An alarm would be triggered if the conductivity is outside a preset range. The allowable range should be supported by cleaning development data.

The optimal *temperature* ranges will vary for the different steps of the cleaning process. Initial solvent rinses are typically performed at ambient temperatures to minimize any denaturation or degradation effects and to maximize the dilution effects. Cleaning solutions may be heated to increase their effectiveness. Final rinse solvent steps may be performed at high temperatures to increase the solubility of cleaning process residues and to increase the drying rate of rinse solvents.

3.3 Design Considerations

3.3.1 Location of Cleaning

Equipment may be cleaned at its installed location, or it may be disassembled and moved to a central location for cleaning.

3.3.1.1 In-Place Cleaning

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. In this document, in-place cleaning can be either for automated or manual cleaning processes.

3.3.1.1.1 Clean-in-Place (CIP) Systems

The term ''Clean-in-Place'' usually refers to an automated system that consists of a system which uses various tanks and piping to deliver a cleaning solution through the equipment to be cleaned. There may be a prerinse tank and a final rinse tank. The CIP system utilizes spraying devices to provide coverage and physical impingement of the cleaning solution on the process equipment surfaces. The sprayballs 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 may be a recirculation system or it may be a single-pass system.

Centralized CIP systems can provide a single location for handling cleaning agents and reduce the plant requirements for cleaning-related equipment (pumps, tanks) and instrumentation. However, centralized systems often require interconnected piping designs and may complicate desires to segregate parts of the process. Some process equipment may require special cleaning agents that are different

than those used for the rest of the process equipment. For these situations, *dedicated* CIP systems that are integrated into the process skids may be desirable.

Design of centralized CIP systems should consider the potential for carryover of product residues between process steps; between products being manufactured concurrently in multiproduct facilities; and between different products after a product changeover. To address the potential for product carryover, central CIP systems are often dedicated to one part of the manufacturing plant. Non-recirculating systems also reduce the potential for product carryover via the CIP equipment itself.

Piping of the equipment being cleaned and of the CIP skid should be sloped continuously to a physical low point to ensure acceptable draining of the lines. If supply and/or return loop headers are used, the loop must be designed such that liquid flows in both parts of the loop at adequate speeds. If this is not achieved, one part of the loop may become a functional deadleg. The pressure drop in the piping also needs to be considered. The CIP skids are often located remotely from the process area, and the length of the distribution piping results in a total pressure drop that can be significant. The greatest challenge is sizing the distribution piping when the supply flow rates in the system have high variability. This has been addressed in some facilities by installing pumps in distribution piping before major equipment to control flow rates. For CIP systems, diameters of drains should be adequate to ensure adequate drainage without a buildup of cleaning or rinse solution in the vessel.

3.3.1.1.2 Solvent Reflux Cleaning

For small-molecule API manufacture by organic synthesis, cleaning may involve boiling a volatile solvent (such as methanol) in the reactor vessel. This is a type of in-place process (but not a CIP system as defined in **3.3.1.1.1).** The solvent vapors rise to other portions of the equipment, and condense on those cooler surfaces. The condensed solvent may dissolve residues on those other surfaces, and carry the dissolved residue back to the boiling solvent in the bottom of the reactor vessel. Such a process is called solvent reflux cleaning. Key issues in solvent reflux cleaning are to make sure that the residues are soluble in the chosen solvent, and the solvent vapors contact and condense on all intended surfaces. The cleaning should also provide an effective rinse of the reactor vessel that held the boiling solvent.

3.3.1.1.3 Placebo Batches as a Cleaning Method

Placebo cleaning is another type of in-place cleaning. For certain highly viscous ointments or products, it may be feasible to use a placebo run as a method of cleaning equipment. This approach requires the use of a placebo that has no detrimental quality impact on the next product manufactured in the equipment. The principle of using a placebo batch for cleaning is that the 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. Therefore, the material would touch the same surfaces and in the same manner as the next product batch. Disadvantages of this method include the cost of cleaning and the difficulty of demonstration of the effectiveness of the process.

3.3.1.2 Out-of-Place Cleaning

Smaller equipment items and portable process equipment that are difficult to clean as installed are often disassembled and transported to a designated cleaning or wash area where the cleaning procedure is performed, either manually or automated. The additional activities involved with transport of equipment to and from the wash room, component identification, and the elimination of the potential for cross-contamination during transfer, reassembly, and storage prior to use makes the validation of these procedures somewhat more complex than the comparable in-place activity. Care should be exercised for routes and means of soiled equipment entering a washing area and routes and means of clean

equipment exiting the washing area, as well as storage of cleaned equipment in the washing area. Care should also be used to assure contact and/or flow of the cleaning agent through all parts of the equipment, such as for lumens or hoses. The need for manual manipulation is an integral part of out-of-place procedures, and generally requires both more detail in the procedures and appropriate training. The manual manipulation makes these concerns similar to those of manual in-place cleaning.

3.3.1.2.1 Clean-Out-of-Place Systems

Clean-out-of-place (COP) equipment includes items such as wash tanks used to clean small parts or parts removed from large equipment. Examples include a recirculating bath used for cleaning small parts, pump components, gaskets and other parts removed from larger equipment. COP systems may also include dishwasher type cabinets where small manufacturing vessels, drums, filter housings or hoppers can be loaded inside the cabinet and cleaned. The placement of the parts, disassembly of equipment and loading patterns are critical to the success of cleaning when using COP systems. The use of these systems significantly reduces the differences between CIP cleaning and COP cleaning, although issues related to disassembly and transport of equipment to the parts washer are still present.

3.3.2 Automated vs. Manual Systems

Three broad definitions of cleaning processes follow, although it should be recognized that they represent points on a continuum. The distinctions between these processes are important to the establishment of an appropriate cleaning process.

3.3.2.1 Manual Processes

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 cleaning personnel.

Important cleaning parameters for manual cleaning may include:

- Volume of cleaning agents
- Volume of rinse water
- Temperature of wash and rinse solutions
- Sequence and duration (contact time) of soaking, wash and rinse steps
- Scrubbing action
- Pressure of solutions
- Detergent concentration

It is important to specify in writing the extent of the equipment disassembly to ensure the reproducibility of the cleaning process. Consistency of manual cleaning over time is accomplished by operator training, adequate supervision, and a well-defined, documented cleaning procedure.

3.3.2.2 Semi-Automated Processes

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 the automated CIP of a tank, or disassembly of a pump or filter housing 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 valves supplying spray balls inside a vessel. This type of cleaning is intermediate between fully automated and fully manual cleaning.

3.3.2.3 Automated Processes

Automated cleaning typically does not involve personnel intervention (except perhaps to select a cycle and the start/stop of the operation). The system is usually programmable for the various cleaning cycles. Use of automation provides consistent and robust control and monitoring of the automated cycles and parameters (such as time, flow rate or pressure, cleaning agent concentration, and temperature).

Important 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 programmable logic controller (PLC). 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 terminal (OIT) 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 is critical to the success of automated cleaning processes.

3.3.3 Soil Evaluation and Categorization

3.3.3.1 Soil Categories

There are a large variety of substances that contact process equipment surfaces during the manufacture of pharmaceutical products. They include manufactured products, degradation products, process aids, solvents, and cleaning agents. Cleaning processes and cleaning validation should be designed and tested to address this wide variety of potential process soils. These tasks may be simplified by creating categories of soils and selecting representative soils for testing and tracking during the development and validation of cleaning processes.

The final selection of a representative soil within a process stream should be based on the similarity of the physiochemical properties of the soils. In many circumstances, categories may be combined and the number of representative soils used for development activities further reduced.

3.3.3.2 Soil Removal

Soils may be removed by physical and/or chemical means. Physical removal may be accomplished by putting energy into the cleaning process through use of high pressure spray, high velocity flow, manual scrubbing, or vacuuming in order to remove soils from the equipment. Physical removal may be dependent on solubility, soil amount and its degree of adhesion to the equipment surface.

Chemical cleaning mechanisms include solubility, emulsification, wetting, chelation, dispersion, hydrolysis and oxidation. Cleaning agents are generally chosen for their ability to remove process soils by one or more of these mechanisms. In some cases, multiple cleaning steps may be used in order to take advantage of different chemical cleaning mechanisms. For instance, alkaline detergent for solubilization and emulsification may be followed by a sodium hypochlorite solution for oxidation of protein soils. It should always be kept in mind that the more aggressive the cleaning solutions are

(e.g., solutions with high concentrations of sodium hypochlorite), the more corrosion may occur. The right choice of materials for cleaning purposes is part of the development phase.

Factors affecting "cleanability" also include the surface geometry, the surface type, the soil type, and the soil level. The ease with which a soil is released from the equipment surface by one of the mechanisms described above determines its cleanability. Soil response to a particular cleaning mechanism may influence the choice of cleaning agent and cleaning conditions. Attachment to surfaces can be by a combination of van der Waals forces, electrostatic effects, and other forces. The time that the soil resides on the equipment can also influence the difficulty of soil removal. Fresh soils are generally easier to remove than soils that have been allowed to dry on the surface. The time between soiling and cleaning must be considered when designing the cleaning studies to simulate the dirty hold time, if applicable. In some cases, difficulty of cleaning does not change with increased dirty hold time. If this is the case and *any* dirty hold time can be used in a protocol, it must be clearly justified and documented.

High soil amounts can complicate removal by saturating the cleaning solvent or depleting surfactants or other components of the cleaner (such as oxidizers or emulsifiers). This may impact the minimum cleaning solution volumes and should be considered in the cleaning cycle design when high soil amounts are anticipated.

3.3.4 Equipment Considerations

Equipment usage during production is another important aspect to consider in designing a cleaning process. It is important to understand the role that the equipment plays in the production train. 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 an important criterion in the design of equipment. 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, and to not contribute possible contamination. 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 baffles, blades, and shafts. Spray patterns may be originally designed by computer simulation, but should be confirmed by a spray coverage test, such as one using a dilute solution of riboflavin.

3.3.4.1 Dedicated – Nondedicated Manufacturing Equipment

Dedicated equipment is used solely for the production of a single product, or in some cases, of a single product line (e.g., containing the same active ingredient). Concerns over cross-contamination with other products are markedly reduced. However, consideration must be given to residues of cleaning agents, degradants, bioburden, and endotoxin.

Where the same piece of equipment is utilized for different product formulations (i.e., nondedicated equipment), the prevention of carryover of active ingredients between products becomes a major focus of the cleaning process. For nondedicated equipment, a design consideration is whether a unique cleaning process will be developed for each manufactured product, or whether one cleaning process will be designed to address all (or a group) of manufactured products.

Certain products (such as beta-lactams) may require segregated production areas. A risk-based analysis

should be performed on other products which may be highly hazardous (e.g., mutagenic active ingredients) in order to determine whether dedicated facilities should be used. For other products, dedication of equipment may be made not on a patient risk basis, but rather as a practical business decision.

3.3.4.2 Nonproduct Contact – Product Contact Surfaces

Validation of cleaning has focused on product contact surfaces. However, indirect product contact surfaces (“nonproduct contact” surfaces with close proximity to open product) may be included in a cleaning validation program. An example of an indirect product contact surface for which cleaning validation is commonly done is a lyophilizer shelf used in lyophilization of vials. Nonproduct contact surfaces such as floors and walls typically have cleaning processes, but those cleaning processes are lower risk, are controlled consistent with GMPs, and are outside the scope of a cleaning validation program. However, cleaning of floors and walls may be addressed as part of an overall cross-contamination program, particularly for highly hazardous drug active ingredients.

3.3.4.3 Low-Risk Sites – High-Risk Sites

Risk is a function of the identification of hazard, the ability to detect that hazard, and the potential exposure of the hazard on product quality and patient safety. Those locations where there is the danger of a residue affecting a single dose with a high level of contamination are high-risk sites. Examples of such sites are a filling needle and a tablet punch. Sites which are difficult to clean are also high-risk sites. Those difficult-to-clean sites may include ports, drains, baffles, and the undersides of agitator blades. These high-risk sites may require special disassembly, cleaning, and/or inspection emphasis. Other sites which are easier to clean and uniformly transfer residue to the next product are generally considered lower risk.

The distinction between ‘‘major’’ and ‘‘minor’’ equipment is not a definitive one. The Good Manufacturing Practice (GMP) ***(6)*** make mention of ‘‘major’’ equipment, but are silent on the subject of ‘‘minor’’ equipment except with regard to items described as utensils. Major and minor designations do not generally reflect the challenge of cleaning, nor define whether the equipment surfaces are a lower or higher risk for cleaning processes. Both major and minor product contact equipment items require cleaning verification or validation for multiproduct equipment.

3.3.4.4 Materials of Construction

Factors affecting “cleanability” include the surface type and the surface finish. The most common surface types encountered are stainless steel and glass, but surface types may include other metals and a variety of plastics and elastomers. Surface finish also affects the removal of soils. Rough surfaces provide more area for soil contact and may contain cracks and crevices that are difficult for the cleaning agent to penetrate. The interior surfaces of stainless steel process equipment may be modified to smooth and/or polish rough surfaces. The materials of construction of the equipment should be considered carefully when designing a cleaning validation program.

Porous materials may require special cleaning processes. Items such as filter bags and filter membranes are typically dedicated to a given product.

3.3.5 Operational Considerations

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

A campaign is a series of batches of the same product manufactured one after the other. Consideration should be given to the need to clean, and the extent of cleaning, between batches in a campaign.

Depending on the product, there may be no cleaning between batches or some level of cleaning is done between batches. If the cleaning between batches is simply a vacuuming (for solid products) or a solvent or water rinse (for liquid products), such cleaning is sometimes called "minor" cleaning or "in-process" cleaning. Such minor or in-process cleaning steps do not require separate validation. However, consideration should be given to the effect of such minor or in-process cleaning steps on the efficiency of the "full" cleaning process done at the end of a campaign for changeover to a new product or campaign.

If only the cleaning process at the end of the campaign is to be validated, consideration should also be given to the number of batches and/or the total elapsed time for a campaign. For example, elapsed time might be critical if the active ingredient left on equipment surfaces degrades over time due to exposure to heat or light. Furthermore, the repetitive production of a single product without validated cleaning between batches might also result in the penetration of materials into a location where single lot production might not present a problem.

3.3.6 Cleaning Agent Selection

Cleaning agent selection should be based on a scientific rationale. Cleaning agents should be selected for their suitability to remove the product residues; their compatibility with equipment; their ease of cleaning agent removal; and low toxicity. Solvents, formulated detergents, and commodity chemicals should be acceptable for the process and for use with pharmaceutical products. Water alone or organic solvent alone may be used as the cleaning agent, particularly for readily soluble soils.

At the time of design of the cleaning process, it is important to review and document information about any cleaning agents to be used. The established cleaning agents should be reviewed against the vendor's current specification sheets and descriptions, including material safety data sheets. 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, as well as the percentage each constituent comprises, that are in the cleaning agent. This allows for the establishment of the consistency of cleaning agent formulation over time, as well as for selecting a possible marker component for analysis of cleaning agent residues.

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, as well as notification of significant changes, should be required of the cleaning agent vendor.

During the development of the cleaning cycle, quantities of cleaning agents, their concentration and their addition mode should 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 *(7)*. Generally, water used for final rinse should be the same grade as used for the manufactured product, e.g., parenteral products should utilize WFI and oral products should employ purified water.

3.3.7 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 ingredients and excipients, possible degradation products and the effect of the cleaning agent are important 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.

3.3.7.1 Product Risk Considerations

The cleaning of equipment is closely tied to the type of materials being removed from the surface. The product formulation (including the active ingredients and excipients and formulation aids), including the nature of the product at various intermediate steps of manufacture, should be considered.

Because limits for highly hazardous drug active ingredients (e.g., those with serious allergenic, cytotoxic and mutagenic properties) are generally more stringent, more robust cleaning processes may have to be designed. Such highly hazardous drug active ingredients may be manufactured on nondedicated equipment provided an appropriate risk analysis and cleaning validation is performed. Some firms may choose to use dedicated facilities and/or equipment for such highly hazardous drug active ingredients even though that might not be a regulatory requirement. Another approach for such highly hazardous drug active ingredients is to include in the cleaning process a deactivation or degradation step such that residues from the active ingredient do not have those properties that make the active ingredient highly hazardous. In addition, any unusual hazards of degradation products (either unintended or intended degradation products) should be considered.

The route of administration of a product may affect the acceptable residue limits, and may therefore affect the nature of the cleaning process. 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 if cross-contamination occurs.

Another risk factor to consider is the amount or extent of information available on the product to be cleaned. For example, the amount of information available for a marketed product may be much more extensive than information on a new drug active ingredient being manufactured for human clinical trials. In addition, in such early clinical manufacturing, a cleaning verification approach may be utilized. With such an approach, the cleaning process may be significantly overdesigned so that after the cleaning process, residue levels are well within acceptance limits.

3.4 Cleaning Development Laboratory Experiments

Laboratory testing often includes screening a combination of soils and relevant process surfaces. Screening experiments are designed to test soil removal capability using representative soils and coupons of relevant surface materials. Cleaning conditions can be selected based on the soil-surface combination encountered in the production equipment.

Laboratory evaluation of the interaction between product and surfaces can be performed using test coupons made of the surface of interest under simulated cleaning conditions. Based on the process details, appropriate materials of construction with the appropriate surface finish characteristics should be selected for use in lab-scale cleaning experiments. To minimize the number of experiments, it may be sufficient to include only those surfaces that are expected to be the most difficult to clean (based on prior knowledge and risk assessment tools). Stainless steel coupons are the most common choice as they often represent a majority of equipment surfaces in a production facility. Non-electro-polished stainless steel coupons with a representative or worse surface finish compared to equipment surfaces may be preferred for lab evaluations.

3.4.1 Soil Selection

Care should be taken in the choice of soils and soil conditions used for selection of cleaning agents during laboratory evaluation. The soils should be representative of the soils on equipment in the manufacturing plant, including the chemical and physical (dried, baked) nature of the soils.

Solutions or suspensions of soils selected for experimentation are generally coated on coupons representing the process contact surfaces and dried to simulate the soil condition on the process equipment prior to testing for removal with cleaning agents. The number of representative soils will vary with an organization's experience and history, as knowledge about the content and cleanability of the various process steps.

Preparation of coupons typically involves use of a cleaning procedure in order to ensure that all coupons are uniformly cleaned at the start of the experiment. This also helps to ensure that any foreign material deposited on the coupon surface during the fabrication process is removed to minimize interference with the process soils or cleaning agent. The coupons are then completely dried before spotting them with soils. It is important that the spotting of soil onto each coupon be kept consistent to minimize experimental variability. The coupons are then dried for a fixed time to simulate the soiled equipment surfaces at the time of cleaning, before they are subjected to the lab-scale cleaning process. That fixed time is generally the desired dirty hold time, or a longer time.

The purpose of the experiment could be to make one or more determinations related to cleanability, including comparison of the various materials of construction for a given soil; different process streams for a given surface; different cleaning conditions (such as concentration of cleaning agent and temperature); different products for the same process step and surface; or a combination of these. The outcome of these studies can be analyzed to create the "design space" for cleaning. In any case, it is important that the performance of the cleaning process in the laboratory represents, as much as practical, the performance in the pilot plant or larger scale process. Important operational parameters such as temperature, time, mode of action and concentration are controlled to mimic what is used in the manufacturing plant. If it is difficult to simulate the actual process conditions in the laboratory, conditions representing a worst-case scenario should be employed. The laboratory studies can also be used to challenge the cleaning process by modifying different variables of the cleaning process to further outline the design space.

Evaluation of performance for cleaning design space studies can utilize the various analytical methods listed in **Section 7.0.**

3.4.2 Parameter Selection

A variety of parameters can impact the performance of a cleaning regimen. These include: nature and strength of the interactions between the product and the surface; nature of the interaction between the cleaning agent and the soil; time (dirty hold time, time for each cleaning cycle); cleaning agent and concentration; temperature; cleaning action [flow properties (stagnant, laminar, turbulent) and pressure]; and properties of the cleaning solution (such as ionic strength, pH, components, viscosity, and density). All of these, except the cleaning action, are independent of the equipment. Selection of parameters to be examined in an experimental study should be done on a case-by-case basis. The larger the number of parameters evaluated, the more the number of experiments may be required to understand the impact of the parameters and their interactions. On the other hand, if critical parameters are not picked, the resulting conclusions in terms of identifying the important operational parameters and their ranges are likely to be erroneous, since important effects might be overlooked.

Use of a risk analysis tool, such as Failure Mode and Effects Analysis (FMEA), may assist with prioritizing the various operational parameters for further examination. Single parameter studies that vary one parameter at a time can be designed to identify the parameters that have significant impact on the performance. One such study conducted at the bench scale reported concentration and temperature of the cleaning solution to be the parameters with predominant effects ***(8).*** As discussed in the following section, single-parameter studies can then be followed by Design of Experiments (DOE) to

investigate the interactions between these parameters. Alternatively, if only a few parameters need to be examined, just performing a DOE to measure both the main effects and the interactions may be more resource- and time-efficient.

3.4.2.1 Parameter Interactions

The use of DOE style experiments helps to determine the effect of varying individual parameters on cleanability as well as providing an indication of their interaction. Statistical tools including regression analysis, leverage plots, response surface analysis and interaction profiles can be used to study both main and interaction effects. Relationships and interactions between parameters, such as temperature of cleaning solution and the concentration of the cleaning agent, may be determined. Such DOE analyses can be used to construct a multi-parameter design space for the cleaning process and to establish the ranges of operational parameters that provide acceptable cleaning process performance.

3.4.3 Measurements to Determine Cleaning Effectiveness

Cleaning effectiveness may be determined by the sampling and analytical methods described in **Sections 6.0** and **7.0.** They include visual inspection, and analytical techniques for measuring any residues, such as of manufactured product, degradant, cleaning agent, bioburden and/or endotoxin. Depending on the purpose and the design/development phase, these may be online and/or offline measurements of rinse or swab samples.

Using existing knowledge and a risk-based approach, cleaning experiments can be reduced or eliminated, e.g., for transfer of a manufacturing process from one facility to another.

3.5 Cleaning Process Scale-Up

Following selection of cleaning agents and cleaning parameter ranges (such as temperature, contact time, cleaning agent concentration, and flow stream hydrodynamics) from historical plant data (if available) and laboratory development work, the cleaning process can be implemented for use on larger-scale manufacturing equipment. Determination of soil and cleaning agent residue removal is generally performed prior to formal cleaning validation protocols. Adjustments to cleaning parameters may be made during the scale-up process based on plant experience and laboratory development studies.

3.5.1 Setting Process Controls

It is both prudent and consistent with current Good Manufacturing Practice (CGMP) to establish control ranges for the cleaning process operational and performance parameters. As appropriate, operational parameters for cleaning processes include:

- Dirty hold time for equipment (time between completion of use and initiation of cleaning)
- Clean hold time for equipment (time between completion of cleaning and next use)
- Flow rate and/or delivery pressure of the cleaning stream (proof of flow for any parallel flow paths)
- Cleaning agent concentration
- Duration of each step in the cleaning process (by time or volume)
- Temperature of washing solutions and rinses
- Air flow verification during any water removal or drying steps

Instrumentation for each of these parameters should be included in the system design. Alert and/or action levels can be set for each critical cleaning process parameter in order to maintain proper operation. Parameters may be significant for business or economic reasons, as well as for patient and product quality reasons, as long as the parameters set for business and economic reasons are more

"stringent" than for patient and product quality reasons. Alert levels may be set based on expected variability of the equipment and instrumentation in the cleaning system. Action levels should be set at values that permit adjustment to the equipment to avoid jeopardizing acceptable operation. Both alert and action levels should be within the acceptable ranges for each parameter. It is also reasonable to establish check times, so that if parameters do not reach their set points (e.g., volume flow, conductivity) within that time, then an alarm or notification occurs.

Performance parameters should also be evaluated during scale-up. As applicable, performance parameters may include:

- Final rinse solvent analysis for active ingredients/degradants
- Final rinse solvent analysis for cleaning agent
- Final rinse water bioburden
- Final rinse water endotoxin

3.6 Applying the "Design Space" Concept to Cleaning Processes

"Design Space" is the multidimensional combination and interaction of input variables and process parameters that have been demonstrated to provide assurance of quality. The Design Space concept has been introduced by the International Committee on Harmonization (ICH) ***(3)*** to describe an approach to the development and control of pharmaceutical manufacturing processes. An analogous approach can be applied to cleaning processes.

The cleaning design space for a manufacturing facility is defined through a risk- and science-based approach relying on cleaning process knowledge, product/equipment knowledge, regulations and quality practices (requirements). Similar to manufacturing process development, control, and validation, cleaning process operational parameters (inputs) can be controlled to ensure predictable and acceptable performance as evidenced by appropriate measurements (outputs). The cleaning design space is represented by the range of each of the operational parameters that results in acceptable performance of the cleaning process.

Steps in defining the design space for a cleaning process may be slightly different from steps taken to define design space for a manufacturing process, in that the design space for a manufacturing process is unique to a given process (e.g., a granulation process). However, many manufacturers may want to design one cleaning process for a specific equipment train that is used regardless of the manufactured product. This may be accomplished by identifying the "worst-case" soils and defining the design space around cleaning process performance using these soils.

Specifications are developed to support the design, installation and operation of the cleaning system. Risks are identified and assessed for impacts to safety and cleaning effectiveness (e.g., severity, probability of occurrence, detectability). Parameters may be categorized based on their level of criticality, with the most critical parameters monitored closely so that the cleaning operation can be corrected if parameters are not kept within their predetermined ranges. The criticality of cleaning process operational parameters is based on laboratory studies and other data/experiences that document the influence of each parameter on cleaning effectiveness.

Cleaning effectiveness may be influenced by the following factors:

- Soil type or family
- Nature of the soil on the surface
- Equipment and contact surface type and finish
- Cleaning technology and functional specifications for the cleaning process.

This information is used to drive the design requirements for the cleaning method. Cleaning validation requires consideration of the worst-case operating conditions. Field conditions such as the flow rate, cleaning agent concentration, contact time, process temperature, and dirty hold time are conditions that are considered when developing an effective cleaning process. The assumption is that any cleaning process that is performed within the space defined by these conditions will be effective, reliable and consistent.

3.7 Standard Operating Procedures

One of the outputs of the design and development of a cleaning process should be a draft Standard Operating Procedure (SOP). That draft SOP should reflect sufficient detail to ensure process consistency. For the draft SOP, the following issues should be considered:

- The maximum allowable hold time for a piece of equipment:
  - after use, but before cleaning
  - after cleaning, but before reuse, sanitization, or sterilization.
- The steps to be taken for 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.
- Critical sites or difficult-to-clean areas that may require special cleaning emphasis or a specific inspection
- Cleaning process parameters
- Assignment of responsibility for cleaning of equipment
- Cleaning schedules, and where appropriate, sanitizing schedules
- Removal or obliteration of previous batch identification
- A description in sufficient detail of the methods, equipment, and materials used in cleaning
- Sampling and testing that is part of the routine cleaning process
- The steps to be taken for reassembling equipment (as necessary) for storage and subsequent use
- Visual inspection for equipment wear, product residuals and foreign materials
- Protection of clean equipment from contamination prior to use
- Batch records as appropriate for the cleaning process. For fully automated processes, the batch record information may be collected and stored as part of the control system. For fully manual processes, the level of detail to be collected for a batch record will depend on the complexity of the process.

3.8 Operator Training for the Cleaning Process

Operator training is critical. During cycle development, operators should be trained in the requirements of the evolving or existing SOPs. Proper training consists of understanding the SOP, demonstration of the correct procedure by a trained operator and demonstration of the correct procedure by the trainee. Operator training for manual cleaning may also include qualification and/or requalification of the trainee by measuring residues on equipment cleaned by the operator. Operator training should be done on a more frequent basis for manual cleaning processes as compared to automated cleaning processes.

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

- Clearly written, understandable and *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.

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 and safety of the next product manufactured in the same equipment.

3.9 Introduction of New Products to a Validated Cleaning System

When new products or significantly different raw materials are introduced to the plant, a system must be in place to ensure that the cleaning process will remain effective.

Generally, the cleaning effectiveness of the existing system for new products can be tested by performing laboratory experiments using coupons of relevant materials (see **Section 3.4** on Cleaning Development Laboratory Experiments). These experiments can be designed to test both the effectiveness of the proposed cleaning regimen and the relative difficulty of cleaning the new soils compared to soils that have already been introduced to the plant. If the new soils are easier to clean than the most difficult soil already being cleaned, introduction of the new material using existing cleaning procedures can be made with confidence. If the material is more difficult to clean than each of the present soils, some modifications to the current cleaning process may be required, and cleaning validation for the new product is an expectation. However, if the new soil is easier to clean, then based on a risk assessment, the number of confirmatory runs needed (if any) is determined.

4.0 Qualification

Qualification is a part of cleaning validation involving the traditional activities of equipment qualification and process qualification. For cleaning validation purposes, equipment qualification focuses on qualifying (or verifying) the equipment used as part of the cleaning process, such as a CIP skid and automated parts washer. For fully manual cleaning operations, such as a brushing or scrubbing, there may be no equipment qualification activities. Design qualification has also been considered as another qualification activity, which is addressed in the design and development stage.

The emphasis for this section is on *process qualification* activities. Process qualification involves the runs performed under a protocol designed to demonstrate the consistency of the cleaning process. The *traditional* approach for cleaning validation has been to focus on the qualification protocols to demonstrate effectiveness and consistency. The *lifecycle* approach that the industry has been moving toward involves a different approach with a more comprehensive view, with qualification runs being only one of the stages of validation. The lifecycle approach also includes design/development activities and validation maintenance (ongoing controls).

This section covers protocol elements and specific important issues for cleaning validation protocols, including the number of validation runs required, mock soiling for validation runs, worst-case process conditions, and the disposition of equipment/product during validation runs. It also covers grouping approaches for products and equipment as well as important considerations in clean hold time studies. It ends with a discussion of documentation for "cleaning verification".

4.1 Protocol Elements

Cleaning validation protocols have many of the same elements as process validation protocols. For reasons of clarity, the *format* of a cleaning validation protocol usually follows the same approach (as appropriate) as used for process validation protocols for a given company. Common elements include (but are not limited to) purpose, validation design/strategy, scope, responsibilities, applicable product(s) and equipment, cleaning procedure and associated documentation, acceptance criteria, training, and a requirement for a final report. Key elements for cleaning validation protocols include residue limits (see **Section 5.0**), sampling procedures (see **Section 6.0**) and analytical methods (see **Section 7.0**).

Two approaches are used for documentation of elements. One general approach is to reference other documents for details regarding that element. For example, specification of swab sampling sites can be in the protocol while the rationale for selection of those sites can be in another document that is referenced in the protocol. The advantage of referencing other documents is that only the detailed information required for executing the protocol is included in the protocol; supporting information is only referenced thus allowing for more "streamlined" protocols. Another approach is to include all relevant details for a given element in the protocol. The advantage of having more details in the protocol is that greater clarity is provided to those executing the protocol. The approach used should consider the knowledge management systems within a given firm.

4.2 Key Protocol Issues

The validation protocol is not written and approved until the cleaning process has been designed and developed (see **Section 3.0**). The execution of the protocol should not begin until the protocol is approved. However, execution of the protocol as an engineering or practice run can be helpful in some circumstances (e.g., for activities that are highly complicated or new to those executing the protocol). Any problems in the execution of the engineering/practice run can be corrected before actual validation runs. The time spent in such runs may lead to the higher likelihood of "right first time" protocol execution for the formal qualification runs.

Key issues for protocols (aside from limits, analytical methods and sampling procedures, which are covered elsewhere) are discussed below.

4.2.1 Number of Runs in a Protocol

The traditional approach for cleaning validation protocols has been to require an evaluation of three *consecutive* runs of the cleaning processes. "Consecutive" means that no cleaning events of that same process are skipped without an appropriate rationale. For example, if the cleaning validation is for cleaning of Product A, there may be manufacture and cleaning of Product B in between manufacture of lots or batches of Product A.

Based on lifecycle approaches to validation, as well as several regulatory documents including the 2011 U.S. FDA process validation guidance, the newer approach has been to provide a rationale, based on an understanding of the cleaning process, documentation from the design and development phase, and data from sufficiently similar cleaning processes, for a specific number of validation runs required ***(9,10)***. This might result in fewer than three runs or greater than three runs. It should be recognized that this new U.S. FDA process validation guidance does not formally cover cleaning validation. However, a number of principles in that document may be applicable to the validation of cleaning processes.

4.2.2 Mock Soiling

Ordinarily a cleaning validation run is performed by cleaning on a commercial-scale batch. An alternative approach is to use what is called "mock soiling" or "artificial soiling" to simulate the nature and condition of the manufactured product on the commercial equipment at the time of initiating the cleaning process. If mock soiling is used, a rationale must be provided for its use as well as why the mock soiling simulates a "realistic" manufacturing situation. A common reason for mock soiling has been to obtain three consecutive cleaning validation runs without being forced to make three commercial-scale batches of the cleaned product. "Mock soiling" (a *process*) should be distinguished from a "mock soil" (sometimes called a "surrogate soil"), which is a *product* which simulates the physicochemical properties of the actual soil.

4.2.3 Worst-Case Process Conditions

The traditional approach for cleaning validation protocols has been to include worst-case process conditions in the three protocol runs. Rationales for worst-case conditions should be given in or referenced in the protocol. For example, worst-case process conditions may include maximum dirty hold time, maximum batches or elapsed time in a campaign, shortest allowed time for manual cleaning steps, lowest allowed temperature for manual cleaning processes, and worst-case circuits for CIP skid selection. Parameters such as temperature, cleaning agent concentration, flow rates, and process step times for *automated* cleaning processes are generally controlled in a *narrow* range such that challenging the cleaning process in the validation runs at the lower or upper end of the specification is not appropriate. If those narrowly controlled parameters are to be challenged in the extremes or outside the specified range, those challenges can be evaluated in development studies to demonstrate the robustness of the cleaning process.

There may be different approaches for addressing worst-case process conditions. In one approach, a worst-case process condition is addressed in each of the required validation runs. An alternative approach is to address a specific worst-case condition in the design and development of the cleaning process such that the cleaning process is developed to address a worst-case condition. Data from such design and development studies may support the use of worst-case conditions in fewer runs.

Another example of worst-case conditions is the number of batches in a campaign where validated cleaning is only performed at the end of campaign. In such cases, there may be no cleaning between batches or there may be only "minor cleaning" (such as vacuuming for solids manufacture or a water rinse for liquids manufacture). In this case, the maximum number of batches may represent the worst case. Therefore, the validation protocol should consider the effect of the maximum number of batches in the campaign.

In such an approach, it may not be feasible to schedule three consecutive campaigns with the same maximum number of batches. One practical way to address this is to manufacture and perform cleaning validation after a specified number of batches that may represent a minimum campaign length. When a campaign involves more than the previous number of batches, a validation protocol is executed on that longer campaign. Data from the longer campaign are then compared with data from the earlier validation runs to determine whether the data are equivalent. The specifics of the results will indicate whether additional validation runs are needed to extend the validated length of the campaign.

A third approach is to address campaign length during the design and development phase. If data or a rationale can be developed to support no change in the difficulty of cleaning *regardless of the campaign length*, then the validation runs can be at any campaign length.

4.2.4 Disposition of Products and Equipment during Validation

A cleaning process generally only affects the next product manufactured in the cleaned equipment. Therefore, following protocol execution the "cleaned" product may be released following company procedures for product release. That release of product is independent of the data obtained for the immediately following cleaning process. The data from that cleaning process is used for the release of the cleaned equipment.

There are several approaches used for disposition of the *equipment* following the cleaning process. One approach is to not release the equipment until acceptable data (including meeting all residue criteria) are obtained for that specific validation run. At that time, the equipment may be safely released for manufacture of the same or another product. An alternative approach is to release the equipment following company procedures *at risk* for manufacture of the next product. However, that next product cannot be released until acceptable data (including meeting all residue criteria) are obtained for that specific validation run. If the cleaning validation run fails to meet its acceptance criteria, then the impact on that specific next manufactured product should be assessed as part of the investigation into that non-conformance. The results of the investigation will determine whether that next manufactured product can be released.

If there are separate validation protocols for equipment items in a train used to manufacture the product on which the validation is being performed, each equipment item can be released based on the protocol data for that validation run for that equipment item. It is not necessary to wait until validation is complete on all equipment items in the train before any item can be released for subsequent manufacture.

4.3 Grouping/Family Approach

Grouping is a strategy whereby manufactured products and/or equipment are considered together, and a formal protocol is performed on a representative from the group. The representative from the group is usually the worst case among products or equipment in a group. Grouping is also called matrixing, family approach or bracketing. The rationale for grouping is to generate optimum value from cleaning validation tasks based on a risk approach. One requirement for grouping is that product and

equipment be cleaned by the *same* cleaning process. The use of *products and equipment* grouping may be used to streamline cleaning validation programs while ensuring sufficient data are available to support the validation of procedures, processes, and equipment associated with cleaning. The grouping program for a given facility or company should be specified or referenced (e.g., by pointing to a facility cleaning rationale) in a well-designed validation program/validation master plan.

4.3.1 Product Grouping

Products may be grouped together if they are manufactured on the same or equivalent equipment, and cleaned by the same cleaning procedure. Products may be assessed for their relative cleanability by several methods. Relative cleanability may be affected by the nature of the active ingredients, of the excipients, and/or of degradation products. One example of assessing relative cleanability involves selecting the product with the least-soluble active ingredient in the cleaning solution. This approach may be appropriate for small-molecule API synthesis cleaned with a solvent or for finished drug product manufacture involving water-soluble formulations. Such an approach may also be possible for solid dosage drug products provided that the excipient portion of the different drug products has the same effect on the difficulty of cleaning. Another approach involves determining relative difficulty of cleaning using laboratory studies. For laboratory studies, cleanability is assessed on coupons or small equipment parts using representative surfaces, with stainless steel being the most common because of its predominance in pharmaceutical equipment. For coupons, the roughness of the surface should be the same or rougher (as a worst case) than actual equipment surfaces. From the lab results, the relative cleanability of each product is defined, typically by determining under proposed cleaning parameters which product requires the longest time to clean. Bioactivity and clinical effects may also be considered for the selection of a representative product.

One option for product grouping is to use a *surrogate* worst-case product. In this situation, the worst-case product is an artificially constructed product (which may not be a commercial product) designed to be more difficult to clean than products expected to be routinely manufactured. One rationale for this approach is to maintain *continuity* of the worst-case product (in cases where a commercial product might be discontinued). Another rationale is to minimize situations in which *new worst-case* products are added.

A qualification protocol on the representative (worst-case) product is performed. The acceptance criterion for that worst-case product is generally the most stringent acceptance criterion of all products in the group (that is, the lowest residue limit). Successful cleaning validation of the representative (worst-case) product means the cleaning of the other products in the group is also validated. Based on risk assessments (addressing both quality risks and business risks), one approach is to perform a single confirmatory validation run on every other product in the group. Also based on a risk assessment, another approach is to perform qualification protocols on both the most difficult to clean product and the product with the lowest limit.

4.3.2 Equipment Grouping

Equipment may be grouped together if they are similar and can be cleaned by the same cleaning procedure. Grouping of equipment is an effective method for encompassing equipment from a limited population of systems undergoing cleaning validation without redundant testing. The grouping strategy is based on designating equipment as "identical" or "similar," based on design, mode of operation, and cleanability. Such a determination usually involves evaluating the equipment qualification, with the stipulation that qualification differences that do not affect the cleaning process may allow one to conclude that two equipment items are *identical for cleaning purposes*. Regulatory documents such as the U.S. FDA SUPAC guidance may assist in that determination ***(11)***.

Once equipment has been placed within a designation, the designation defines the cleaning validation requirements. If it involves *identical* equipment, a protocol involving any combination of identical equipment items in the group is performed. Provided an adequate rationale is given for determining the equipment items are identical, there is no need to perform validation runs on *every* item in the group. For *similar* equipment, the representative equipment is the worst case or may involve bracketing of the equipment. For example, for storage tanks that are of the same size but different complexity due to the number of baffles, the more complex equipment is chosen as the worst case. For similar equipment of different sizes, the largest and smallest (representing the extremes) may be chosen for the formal validation runs (*unless* one size can be determined as the worst case). If there is no worst case or bracketing involved, then any equipment items in the group of similar items may be chosen for validation runs. Confirmatory validation runs (perhaps only one run) are an *option* for other equipment (not a worst-case) within the group.

A specific case of equipment grouping involves "minor" equipment, such as utensils, small parts, and smaller equipment. In the case of such minor equipment, it may be appropriate to evaluate a cleaning procedure for those parts and to validate the cleaning process using equipment grouping. The grouping of the parts may involve selection of worst-cases based on complexity, size and functionality.

4.3.3 Introduction of a New Product or Equipment into a Group

The introduction of a new *product* into an already validated group is assessed using the *same* science and risk-based evaluation process (e.g., based on solubility in the cleaning solvent, a laboratory coupon study, and/or information from other process cleaning studies) to initially determine the worst-case product. It is recommended that if each new product is tested in a lab evaluation, a suitable control, such as the previous worst-case product, be included. Relative product cleanability is then used to determine validation requirements for that new product on equipment used for other products in that group. The relative cleanability of the product in relation to the preceding worst-case product, as well as any change in the lowest limit for products in the group, will dictate the validation requirements. Based on a documented risk assessment, introduction of an *easier-to-clean* product may just require laboratory and/or scale-up studies to confirm ease of cleaning or may require one confirmatory run. Introduction of a *more difficult-to-clean* product requires validation of that new worst-case product.

Based on risk considerations, introduction of new *identical equipment* may simply involve a determination that it is equivalent or may require an additional confirmatory run. Introduction of new *similar* equipment requires an evaluation if that new equipment represents a new worst case or a new bracketing extreme. If not a new worst case or new extreme, special attention should be paid to the first commercial cleaning event to confirm effectiveness. If the new equipment is a new worst case or bracketing extreme, the validation requirements for the previous worst case or bracketing extreme should be performed for the new worst-case or bracketing extreme equipment.

4.4 "Cleaning Verification" Documentation

"Cleaning verification" as used in this Technical Report refers to documentation which says that a one-off cleaning event is effective for cleaning equipment so that the equipment can be used for subsequent manufacture of a product. There may be a variety of other terms for this same concept that are used by various companies. Examples of where cleaning verification might be used include cleaning after manufacture of a clinical trial product or cleaning after product manufacture where there is a deviation (e.g., the dirty hold time is exceeded) that affects a validated cleaning processes.

Documentation for *cleaning verification* purposes is similar to the documentation for cleaning validation, except that the verification data is *specific to one cleaning event*. From a compliance perspective,

the data applies only to the one cleaning event (although from a scientific perspective the data may suggest similar performance if the cleaning event were repeated). Another difference is that because cleaning verification is typically performed on a unique cleaning event, there may be limited cleaning design and development before execution of that event. One approach is to utilize a cleaning SOP and a cleaning verification protocol. Alternatively, companies might use a concept that defines explicit requirements for cleaning verification in an SOP and documents the specific activities, sample positions and so on in a form which will be approved. It is generally not appropriate to consider three cleaning verification runs as constituting a "validation" especially if the element of appropriate design and development is absent.

5.0 Residue and Limits

Based on the understanding of the cleaning process, potential residues remaining on equipment surfaces after cleaning can be identified. Residues may include the active drug, excipients, processing aids, cleaning agents, bioburden, endotoxin, and degradants. Those residues, if present at unacceptable levels and could potentially contaminate or adulterate the next manufactured product, should be identified. Based on a risk assessment, residues are selected that will be measured in a cleaning validation protocol, and for which limits should be established. Typically for non-sterile manufacturing, this includes the drug active, the cleaning agent and bioburden. Typically, for sterile manufacture, endotoxin should also be included. Other potential residues may be added to this list based on the risk assessment. Furthermore, based on a process understanding and risk assessment, it may be acceptable to not set limits for potential residues in this list. For example, in non-sterile manufacturing, setting limits for and measuring bioburden in a protocol may not be required if there is a final wipe or rinse of equipment surfaces with a sanitizing or disinfecting agent, such as 70% isopropanol, provided there is a scientific rationale and/or supporting laboratory studies.

The determination of cleaning limits and acceptance criteria is a crucial element of a cleaning validation program. A limit is typically an actual numerical value and is one 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 a qualified analytical procedure. In addition, the limits must be achievable by the cleaning process for the product and by the analytical methodology available for the target residue. Finally, the company should develop a scientifically sound rationale for the limits chosen. It is very important that cleaning limits not be selected arbitrarily but rather there be a logical and scientific basis for the limits selected. The scientific rationale should be appropriately documented and should be logical, comprehensive, and readily understood.

5.1 Considerations for Developing Limits

As used in this Technical Report, "product" may be drug product, API, intermediate, or another type of formulation. If "drug product" is intended, that terminology will be utilized.

Residues remaining on equipment may transfer to a subsequently manufactured product. Thus, it is important to have information about the potential residues as well as the product which could become contaminated. Furthermore, the nature of the cleaning process itself is also important. Once these areas have been considered, it is important to obtain a cleaning process understanding (e.g., through process mapping), and then to perform a risk assessment for the appropriate evaluation of limits.

Relevant information for the *subsequently manufactured* product may include, as appropriate for the nature of the product (drug product, API, or intermediates), the formulation, the product's specifications, the dosing, the route of administration, the batch size, and the shared equipment. Product specifications may be important, e.g., for establishing bioburden limits. Relevant information on the *cleaned product* includes the formulation, the dosing, the toxicity, and the route of administration. Relevant information on the cleaning process includes the cleaning agent, cleaning method, and the various cleaning parameters (see **Section 3.0** on design and development of cleaning processes).

5.2 The Basis for Quantitative Limits

Limits are usually based on one of the following as described in later sections:

- The medical or pharmacological potency of the drug active
- The toxicity of the residue
- A default value

Different manufacturing and cleaning situations may require different approaches. For example, for in vitro diagnostics, the effect of the residue on the stability or performance of the subsequently manufactured product may provide a better scientific rationale for establishing limits. The following section discusses the basis of typical carryover calculations. Depending on the manufacturer, the expression of those calculations may be different because it may combine various steps given below. However, it is critical that the units used in the equation be internally consistent; for this reason, unit conversion factors (e.g., grams to micrograms) may be utilized in these equations. In addition, companies may use different terms (or acronyms) for the same concept but still apply the same basic principles in calculations; this is to be expected in a field as diverse as cleaning validation.

5.3 Acceptable Concentration of Residue in Next Product

The first determination is the acceptable level (i.e., concentration) of the target residue in the subsequently manufactured product. This may be called by different terms, but for this document that concentration will be called Acceptable Residue Level (abbreviated ARL). This is an expression of the maximum concentration of residue allowed in that next product, as determined by medical, pharmacological, safety, stability and/or performance issues. For chemical residues (such as the drug active or cleaning agent), this concentration is typically given as µg/g or µg/mL (or an equivalent expression depending on the units selected). For bioburden, this is typically given as colony forming units (CFU), CFU/g or CFU/mL.

5.3.1 ARL Based on Drug Active Dose

For drug actives in *drug product manufacture*, this is typically determined as one-one thousandth (0.001) of minimum daily dose of the drug active in a maximum daily dose of the next drug product. This approach is an alternative to the acceptable daily exposure (ADE) (see **Section 5.3.2.1**) approach for non-highly hazardous active ingredients for manufacture in nondedicated equipment. This is expressed in the following equation:

[Equation 5A]

$$ARL = \frac{MDD \times SF}{LDD}$$

Where:

ARL = the acceptable residue level in the next drug product

MDD = the minimum daily dose of the *active* of the cleaned product

SF = the safety factor, which is typically 0.001

LDD = the largest daily dose of the next *drug product* to be manufactured in the same equipment

[Note 1: For *API manufacture*, where both the cleaned product and the next manufactured product are APIs, **Equation 5A,** as well as other applicable equations in **Section 5.3,** is modified with LDD being the largest daily dose of the next drug *active* manufactured in the same equipment**.]**

[Note 2: For MDD, another approach is to use the single therapeutic dose rather than the minimum daily dose. The use of a minimum daily dose has a scientific rationale based on normalizing the dos-

age frequency for the cleaned product and the next product. For products administered daily, the use of a single therapeutic dose may be more stringent so it is an acceptable practice. However, if the cleaned product is administered once a week, and the next product is administered once a day then the use of a single therapeutic dose in place of the MDD will result in patients who take the next product receiving 0.001 of a single weekly dose taken on a weekly basis. Therefore, in the latter case, it is preferable to compare both products on the same basis, either weekly or daily (convert a daily dose to a weekly dose by multiplying by 7, or convert a weekly dose to a daily dose by dividing by 7)**.]**

[Note 3: Another approach is to express the safety factor (SF) as 1000 rather than 0.001. In such cases, SF will be in the denominator of **Equation 5A.]**

5.3.2 ARL Based on Toxicity

There are typically two types of calculations based on the toxicity of the residue for either drug product or API manufacture.

One approach is the Risk-MaPP Acceptable Daily Exposure (ADE) approach ***(12)***, which may be applicable to residues of drug actives, intermediates, and degradants. The limit is generally based on a No Observable Adverse Effect Level (NOAEL) or other relevant toxicological data. For highly hazardous drug actives, using the ADE approach is generally required in order to justify manufacturing those active ingredients in nondedicated equipment. For non-highly hazardous drug actives, the ADE approach is an alternative to the dose-based approach (see **Section 5.3.1).**

A second approach may be the use of LD_{50} values for limits for residues like cleaning agents which do not have a dose.

5.3.2.1 ADE Determinations Based on ISPE's Risk-MaPP

The safe daily amount in this approach is called the ADE. The first step is to identify the NOAEL for that chemical (usually in an animal study or from relevant human data) by evaluating the response that makes the chemical hazardous. An ADE is estimated by a qualified toxicologist based on the body weight and a variety of adjustment factors as given in Equation 5B. While the ADE definition specifies safety by *any* route of exposure, use of an ADE for a specific and relevant route of exposure is also allowed; this *may* allow for higher ADE value provided that the potential exposure is limited to that specific route of exposure.

[Equation 5B]

$$ADE = \frac{NOAEL \times BW}{UF_C \times MF \times PK}$$

Where:

NOAEL = No Observable Adverse Effect Level

BW = body weight of patient taking next product

UF_C = a composite uncertainty factor determined from such factors as interspecies differences, intraspecies differences, subchronic to chronic extrapolation, LOAEL to NOAEL extrapolation, and database completeness

MF = a factor based on the judgment of the toxicologist

PK = a pharmacokinetic factor to account for different routes of exposures

The ARL for drug product manufacture is then calculated by the following equation:

[Equation 5C]

$$ARL = \frac{ADE}{LDD}$$

Where:

ARL = the acceptable residue level in the next drug product

ADE = Acceptable Daily Exposure of the residue

LDD = the largest daily dose of the next drug product to be manufactured in the same equipment

[Note: For API manufacture, the LDD value is the largest daily dose of the next drug active manufactured in the same equipment**.]**

5.3.2.2 Toxicity Calculations Based on LD_{50} Data

This approach is used for residues where the relevant data are short-term toxicity studies, such as a LD_{50} study. Examples of such residues include cleaning agents and intermediates. In this case, the NOEL is estimated from the LD_{50} value using the following equation:

[Equation 5D]

$$NOEL = \frac{LD_{50} \times BW}{MF1}$$

Where:

NOEL = No Observable Effect Level

LD_{50} = the 50% lethal dose of the target residue in an animal, typically in mg/kg of body weight (by the appropriate route of administration)

BW = body weight of patient taking next product

MF1 = modifying factor or factors, selected by the toxicologist

The cumulative modifying factors selected are generally no more than 1000.

Once the NOEL is estimated, the SDI is determined by **Equation 5E.**

[Equation 5E]

$$SDI = \frac{NOEL}{MF2}$$

Where:

SDI = Safe Daily Intake of the residue

NOEL = No Observable Effect Level

MF2 = modifying factor or factors, selected by the toxicologist

The cumulative modifying factors selected are generally no more than 1000.

Once the SDI is established, the ARL is determined by **Equation 5F.**

[Equation 5F]

$$ARL = \frac{SDI}{LDD}$$

Where:

ARL = the acceptable residue level in the next drug product

LDD = the largest daily dose of the next *drug product* to be manufactured in the same equipment

In **Equations 5D** and **5E,** the modifying factors can be based on one of several published references ***(13-15)***. An alternative approach for this series of calculations is to combine **Equations 5D, 5E** and **5F** into one equation for determining the ARL directly.

5.3.3 Other ARL Determinations

For residues which are genotoxic, one alternative approach used when the NOEL values are not available is to determine the SDI using the Threshold of Toxicological Concern principle ***(16)*** which, based on an U.S. FDA determination about safe levels in foods, is established at 1.5 μg/day. While this may be appropriate for oral doses, it may not be appropriate for injectables since the U.S. FDA determination was based on safe levels in foods (which are taken orally). The ARL is expressed in the following equation:

[Equation 5G]

$$ARL = \frac{SDI}{LDD}$$

Where:

ARL = the acceptable residue limit in the next drug product

SDI = the safe daily intake of the residue

LDD = the largest daily dose of the next drug product to be manufactured in the same equipment

For residues for which the concern is a possible deleterious effect on stability, performance or efficiency of a subsequent product or process, the ARL must be determined directly based on an understanding of the products, the process, and the expected effect. For example, for an in vitro diagnostic, the acceptable level of residue of a previous product may be determined based on the effect on stability or performance of that next in vitro diagnostic. That level may be determined by spiking studies of residue in the in vitro diagnostic to determine effects on stability and/or performance (e.g., false positives or false negatives).

5.4 Acceptable Total Carryover

Once the ARL is determined, the maximum allowable carryover (MAC or MACO) can be calculated. MAC is the total amount of a target residue allowed in a batch of the next manufactured product. It is calculated by multiplying the ARL by the minimum batch size of the next product. MAC, which may be expressed in mass units for chemical residues (e.g., μg or mg or g), is expressed in the following calculation:

[Equation 5H]

$$MAC = ARL \times MBS$$

Where:

MAC = the Maximum Allowable Carryover

ARL = the Acceptable Residue Limit in the next product

MBS = the Minimum Batch Size of the next product

Note that the minimum batch size is typically expressed in mass units if ARL is expressed as μg/g or in volume units if ARL is expressed as μg/mL. For API manufacture, where both the cleaned product and the next manufactured product are APIs, **Equation 5H** is modified with MBS being the minimum batch size of the next drug active manufactured in the same equipment

Because the MAC is the total amount allowed in the next manufactured product, it is also the total amount allowed on shared equipment surfaces (that is, shared between the cleaned product and the next manufactured product).

5.5 Surface Area Limit

Once the MAC is determined, the surface area limit (SAL) can be calculated by dividing the MAC by the *total* equipment shared surface area between the two products. SAL, which may be expressed for chemical residues in mass units per surface area (e.g., μg/cm^2), is expressed in the following calculation:

[Equation 5I]

$$SAL = \frac{MAC}{SSA}$$

Where:

SAL = the Surface Area Limit (on shared equipment surfaces)

MAC = Maximum Allowable Carryover

SSA = Shared Surface Area

5.6 Limit in Protocol Samples

Once the SAL is determined, the limit in swab or rinse samples can be calculated. Three typical cases of limits in samples are covered below.

5.6.1 Limit per Swab

For swab sampling, one approach is to express the limit as a mass-per-swab sample (e.g., μg of residue per swab or μg/swab). The mass-limit-per-swab is determined by multiplying the SAL by the area sampled (typical swab sampling areas are 25 cm^2 and 100 cm^2) ***(17).*** This is expressed in the following calculation:

[Equation 5J]

$$\text{Limit per swab} = SAL \times \text{swabbed area}$$

Where:

SAL = the Surface Area Limit (on shared equipment surfaces)

5.6.2 Concentration Limit in Extracted Swab Solvent

For swab sampling, another approach is to express the limit as a concentration of the residue in a fixed amount of solvent (aqueous or organic) used for extracting the swab. The concentration limit is typically expressed in units such as μg/g, μg/mL or ppm. This concentration limit is determined by multiplying the SAL by the area sampled, and then dividing the result by the amount of solvent used for extracting the swab (in g or mL). This is expressed in the following calculation:

[Equation 5K]

$$\text{Concentration Limit} = \frac{SAL \times \text{swabbed area}}{SEA}$$

Where:

SAL = Surface Area Limit (on shared equipment surfaces)

SEA = Solvent Extraction Amount

5.6.3 Concentration Limit in Rinse Sampling Solution

For rinse sampling, most companies express the limit as a concentration of the residue in a fixed amount of the rinse sampling solution. This concentration limit is typically express in units such as μg/g, μg/mL or ppm. This concentration limit is determined by multiplying the SAL by the area sampled by rinse sampling and then dividing the result by the amount of rinse solution used for the sampling rinse (in g or mL). This is expressed in the following calculation:

[Equation 5L]

$$\text{Concentration Limit} = \frac{\text{SAL} \times \text{Area Sampled by Rinse Sampling}}{\text{Rinse Sampling Volume}}$$

Where:

SAL = the Surface Area Limit

If the entire equipment train is rinsed with one rinse solution, then the SSA and the "Area Sampled by Rinse Sampling" are identical. Therefore, a simplified expression for the concentration limit in the rinse sample (avoiding the need to determine the SSA) is:

[Equation 5M]

$$\text{Concentration Limit} = \frac{\text{MAC}}{\text{Rinse Sampling Volume}}$$

5.7 Consolidated Expressions

While the calculations in **Sections 5.3** to **5.6** are presented to explicitly show the steps in quantitative calculations for limits, it is common for companies, based on an understanding of their cleaning validation practices, to combine several equations together to simplify calculations. For example, companies that set limit for a drug active primarily on a fraction of the therapeutic dose may address all the factors in **Equation 5A** and **5H** with an overall equation for MAC as follows:

[Equation 5N]

$$\text{MAC} = \frac{\text{MDD} \times \text{SF} \times \text{MBS}}{\text{LDD}}$$

Where:

MAC = Maximum Allowable Carryover

MDD = the minimum daily dose of the active of the cleaned product

SF = the safety factor, which is typically 0.001

MBS = the Minimum Batch Size of the next product

LDD = the largest daily dose of the next drug product to be manufactured in the same equipment

Other companies that set limits for drug active primarily on a fraction of the therapeutic dose may address all the factors in **Equations 5A, 5H, 5I,** and **5K** with an overall equation for the concentration limit in an extracted swab sample as follows:

[Equation 5O]

$$\text{Concentration Limit} = \frac{\text{MDD} \times \text{SF} \times \text{MBS} \times \text{swabbed area}}{\text{LDD} \times \text{SSA} \times \text{SEA}}$$

Where:

MDD = the minimum daily dose of the active of the cleaned product

SF = the safety factor, which is typically 0.001

MBS = the Minimum Batch Size of the next product

LDD = the largest daily dose of the next drug product to be manufactured in the same equipment

SSA = Shared Surface Area

SEA = Solvent Extraction Amount

5.8 Example Calculations

As an example of an overall calculation of a MAC limit based on a fraction of a therapeutic dose, we use the case of the cleaned drug product having a daily therapeutic dose of 100 mg of the active. If the next drug product to be manufactured in the same equipment has a batch size of 10 kg, and a largest daily dose of 800 mg, then using a safety factor (SF) of 0.001, the calculation (using **Equation 5N**) would be:

$$\text{MAC} = \frac{\text{MDD} \times \text{SF} \times \text{MBS}}{\text{LDD}}$$

$$= \frac{100\ \text{mg} \times 0.001 \times 10{,}000{,}000\ \text{mg}}{800\ \text{mg}} = 1250\ \text{mg}$$

This is the total limit for all residues of the specified active on all shared equipment between the two products.

Below is a second example of an overall calculation of a concentration limit in an extracted swab sample, again using the case of the cleaned drug product having a daily therapeutic dose of 100 mg of the active. The next drug product to be manufactured in the same equipment has a batch size of 10 kg and a largest daily dose of 800 mg, and a safety factor of 0.001. If the shared surface area is 250,000 cm^2, the swabbed area 100 cm^2, and the amount of solvent used for extraction of the swab is 5 mL, then the calculation (using **Equation 5O**) would be:

$$\text{Concentration Limit} = \frac{\text{MDD} \times \text{SF} \times \text{MBS} \times \text{swabbed area}}{\text{LDD} \times \text{SSA} \times \text{SEA}}$$

$$= \frac{100\ \text{mg} \times 0.001 \times 10{,}000{,}000\ \text{mg} \times 100}{800\ \text{mg} \times 250{,}000 \times 5}$$

$$= 0.1\ \text{mg/mL (or 100 μg/mL)}$$

5.9 Other Considerations

The items discussed below are issues that may be considered as part of any evaluation in establishing limit.

5.9.1 Multiple Next Products

In many pharmaceutical manufacturing situations, there is not just one product that could possibly be manufactured after a given product for which limits are being established. If flexibility is desired to manufacture products in any order, calculations should be considered for all "subsequently manufac-

tured products", and the resulting lowest limit (typically the lowest limit per surface area) should be established for the cleaned product. As discussed previously, relevant factors to consider for the next product are dosing, batch size and shared surface area. In this manner, any of the products considered may be safely manufactured after cleaning of the first product. In such evaluations, the combination of the specific relevant factors for each next product should be considered. However, it is also acceptable as a worst-case to consider only the most stringent of each of the three relevant factors.

Another option is to restrict the order of manufacturing based, for example, on a specific subsequently manufactured product causing a limit to be very low. In such cases, procedures should be in place to assure that the restricted order of manufacture is consistently followed.

A third option is to operate in cleaning verification mode where the acceptability of each specific cleaning event is determining based on a limit for the immediately following next product. In this way, the limit for cleaning a given product may vary depending on subsequently manufactured product. In this verification mode, residues are measured after each cleaning event and compared to the acceptance limit calculated based on the product immediately following.

5.9.2 Next Product in Verification Approach

In a cleaning verification protocol, only the actual *immediately following* product is required for establishing limits. Particularly in development or clinical manufacturing, where a verification approach is commonly used, the next product may not be known *at the time of the cleaning verification evaluation*. In such cases, one approach is to measure residues following cleaning, and then not to release the equipment until the next product is determined. At that time, a carryover evaluation is performed to determine whether the residues measured are acceptable. If the measured residues are not acceptable, the equipment may be recleaned and cleaning verification performed again. A second approach is to establish, based on the types of products manufactured, some worst-case values for the relevant factors for the next product. These worst-case values are used for establishing limits, and the equipment is cleaned to meet those values. When the next product is determined, it is appropriate to verify that the relevant parameters of the next product are within the worst-case values.

5.9.3 Default Limits

As used in this document, default limits are one of two types. One type is a default limit which is utilized if the default value is more stringent than what is established by the medically safe calculation (as given in **Sections 5.3** through **5.8).** A second type is a default limit where a medically safe limit cannot be established, such as for intermediates in API manufacture. In the latter case, the default limit may be established on criteria that are specific to the individual situation, based on process understanding and a risk assessment.

One example of the first type of default limit is a default limit used *for the ARL*. For drug products, the most common default limit for the ARL (the limit in the next product) is 10 ppm; however, other values may be used. If the ARL calculation (**Equation 5A, 5D** or **5F**) results in a value above 10 ppm, then 10 ppm is used as the ARL. If the ARL calculation results in a value below 10 ppm, then that lower calculated value is used as the ARL. For API manufacture, more common default limits for the ARL are 50 ppm or 100 ppm ***(18)***, although other values may be selected and used if they are more stringent than what is established by the medically safe calculation.

A second example of this type of default limit is a default limit for the SAL. For either drug product or API manufacture, the most typical default value for the SAL used is $4\mu g/cm^2$. This level is commonly cited as the upper limit for what is considered visually clean. If the SAL calculation (**Equation**

5I) results in a value above 4 μg/cm², then 4 μg/cm² is used as the SAL. If the SAL calculation results in a value below 4 μg/cm², then that lower calculated value is used as the SAL.

It should be understood that in these two examples, the logic is that any value below the *medically safe* value may be used as it represents a more stringent criterion.

5.9.4 Use of Different Safety Factors

The safety factor applied to a minimum daily dose is typically 0.001 (one one-thousandth), regardless of the route of administration. Based on a risk assessment, a more stringent or less stringent safety factor may be applied as appropriate for a specific situation. For example, for clinical trial materials where the dose is not fully established, a more stringent safety factor may be considered. Since the safety factor of 0.001 was originally established for drug product administered chronically, it may be acceptable (again based on a risk assessment) to use a less stringent factor for drug products administered for a short time (such as cold tablets, which may be administered for only 10 days).

5.9.5 Different Routes of Administration

If the cleaned product and the next product are administered by different routes (such as the first product being an oral dose and the second product being an injectable), a risk assessment should be considered. This risk assessment might include an evaluation of hazards of the oral drug if administered as an injectable, or it might include a review of data for the extent of systemic availability of the oral drug if given orally.

5.9.6 Different Doses for Adults and Children

For two products where both products have different doses for adults and for children, it is appropriate to determine the ARL based on both products with the adult dose, and then for both products using the child's dose. The lower ARL of the two values should be used for subsequent limit calculations. In cases where one product may be dosed only for adults and the next product only dosed for children, then a risk assessment should be considered.

5.9.7 Human and Veterinary Products Manufactured on the Same Equipment

For this situation, a risk assessment should be considered to set limits appropriately. In addition to the species difference, the body weight difference may also be a significant factor.

5.9.8 Residues of Genotoxic and Other Highly Hazardous Active Ingredients

One approach to genotoxic residues is covered in **Section 5.3.3,** which is to utilize the Threshold of Toxicological Concern (TTC) value of 1.5 μg/day as the safe daily intake ***(16)***, and utilize conventional calculations to set an acceptable limit in an analytical sample. Another approach for genotoxic residues (provided the genotoxic residue is the active ingredient and not a degradant), as well as other residues of special medical concern, is to dedicate equipment to that one product and thus avoid the issue of the genotoxic residue being carried over to a different product. A third approach is to perform cleaning validation, with limits based on a toxicological evaluation related to the genotoxic effect (or other special toxicity concern) using the principles in **Section 5.3.2.2.** A fourth approach is to set the limit for the genotoxic residue as below the limit of detection of the best available analytical technique. In the latter case, a medical risk assessment should be performed to determine whether residues *at that detection limit* are acceptable. In this latter case, it may also be possible to include in the cleaning process a step which deactivates or degrades the genotoxic material such that genotoxic properties are no longer present. Such a determination of deactivation or degradation is preferably performed as a laboratory study. These approaches may also be applicable to other active ingredients with special concerns, such

as reproductive toxicity hazards, allergenicity, cytotoxicity, and mutagenicity.

5.9.9 Limits Based on Analytical Detection Limits

Limits may be established based on the analytical detection limits providing residues at those analytical detection limits are determined to be safe. It should be recognized that this method is not normally recommended because with ever improving analytical methods, the limits will be driven exceedingly low so as not be practically achievable. The issue is not whether the residue can be measured, but rather whether the residue is medically safe and does not affect subsequent product quality.

5.9.10 Degradation of the Active Ingredient

If the active ingredient degrades during the cleaning process (or after the cleaning process during the time before sampling), it may not be appropriate to measure residues of that active ingredient using a specific analytical procedure in a cleaning validation protocol. The reason is that the relevant residue to measure is the degradant. There are at least two approaches to dealing with this situation. One approach is to set limits for the degradant, and then measure the degradant in the protocol using an appropriate analytical method. This assumes that there is a specific degradant for which limits can be established (e.g., based on a toxicity calculation). Another approach is to set limits for the undegraded active based on its dose. Residues are then measured with a nonspecific analytical method (such as TOC). The residue as measured by that nonspecific method is converted to an equivalent amount of undegraded active ingredient and compared to the calculated limit. This approach may be acceptable if the safety concerns from residues of the degradant(s) are no more serious than the safety concerns of the active ingredient. There may be other acceptable approaches based on the specific of the situation and a risk assessment.

5.9.11 Limits Not Measureable

If calculations for the limit of the active ingredient in the analytical sample result in values that are not measurable by available analytical methods, there are several options. One option is to dedicate the equipment to that one product, thereby reducing the need to measure the active ingredient except by a visually clean criterion. A second option is to modify the parameters of the next manufactured product such that the limit is higher. For example, raising the minimum batch size of the next product will increase the limit. It may also be possible to restrict the order of manufacture such that certain products, which drive the limit lower, are not manufactured after the cleaned product with the low limit. In such cases, appropriate measures should be put in place to insure that only those approved products are manufactured as the next product. A third option is to modify the sampling parameters. For example, for swab sampling, sampling a larger area (100 cm^2 rather than 25 cm^2) or extracting the swab with a smaller amount of solvent will result in an increased limit in the analytical sample. A fourth option is lower the rinse volume for rinse sampling. A fifth option is to concentrate the rinse sample by a technique such as vacuum evaporation.

5.9.12 Limits for Organic Solvents

For organic solvents that are typically used for cleaning in small molecule API synthesis, limits may be established based on toxicity calculations. Another approach is to use the values in ICH Q3C (R5), which establishes acceptable levels for solvents in API's and in drug products ***(19)***. It should be recognized that Q3C technically applies to solvents used in the *manufacture* of API's. While cleaning processes are sometimes considered manufacturing steps, they are often considered part of the supporting "equipment and facilities". Therefore this approach should be carefully evaluated before use. Another approach is not to set limits for volatile organic solvents. One situation where this may apply is if there is an adequate determination (based on process understanding and appropriate studies) that there are adequate conditions for the volatile solvent to evaporate. Note that this latter consideration also applies to use of isopropanol or ethanol used as final rinse or wipe for drug product manufacture.

Another situation where limits may not be required is where the same solvent is used for the final rinse as for manufacture of the next product.

5.9.13 Dedicated Equipment

For equipment trains dedicated to manufacture of only one product, the concern about carryover of the active ingredient from one batch to the next is minimized. As stated in the U.S. FDA guidance document, visually clean may be appropriate to address such a concern ***(20)***. However, cleaning validation may still be required because of concerns about other residues, such as degradants, cleaning agent and bioburden, carrying over to the next batch of the same product.

If only parts of an equipment train are dedicated to one product, then that dedicated part is not considered as part of the shared surface area for calculating limits for an active ingredient. However, the surface area of that part may be relevant for calculating other limits, such as the limit for the cleaning agent.

Another approach is to set limits for the active ingredient and measure residues of the active ingredient in a cleaning validation protocol for dedicated equipment for other reasons, such as concerns about batch integrity or certain equipment surfaces may not be easily evaluated by visual examination.

5.9.14 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. The MAC is the sum of all target residues that could be present on the various pieces of relevant shared equipment surfaces. A common practice is to require the same SAL for each and every surface in an equipment train. An alternative is to apportion the total amount (the MAC) differently among the different equipment items, such that the total amount present still reflects the MAC amount. For example, for an equipment train comprising three separate vessels each of the same surface area, the SAL limit might be 1.0 $\mu g/cm^2$ if the MAC is distributed evenly over all surface areas. In contrast, the MAC might be apportioned such that the SAL was 0.5 $\mu g/cm^2$ for Equipment A, 1.0 $\mu g/cm^2$ for Equipment B, and 1.5 $\mu g/cm^2$ for Equipment C, provided the total carryover limit was still at the calculated MAC value.

5.9.15 Limits for Preferential Transfer to a First Portion of the Next Product

An equipment train should be delineated to separate those portions in which the residue would be evenly (homogeneously) distributed in the next product (e.g., blender, granulator) from those in which the residue could be transferred to an individual dosage unit of the next product (e.g., tablet press, vial filler). To address the situation of preferential (non-homogeneous) transfer, the carryover calculations can be adjusted based on the surface area subject to preferential transfer and the portion of the next batch subject to being potentially contaminated with the transferred residue. This will result in using a different, more stringent limit to the equipment surfaces which can preferentially transfer to the next product, thus restricting potential carryover to an initially manufactured single product dose of the next product. In addition, this preferential transfer can be addressed based on production techniques if an adequate first portion of the next manufactured product (e.g., filled vials, tablets) is discarded. Another option is to utilize equipment parts dedicated to one product where this preferential transfer may occur.

5.9.16 Limits for Biotechnology Manufacture

More information on limits for biotechnology manufacture is given in PDA Technical Report No. 49, "Points to Consider for Biotechnology Cleaning Validation" ***(2)***.

5.9.17 Products with More Than One Active Ingredient

In drug product manufacture, there may be more than one active ingredient in the drug product. In such cases, there are at least two options. One option is to set limits for all active ingredients and measure each active ingredient in a cleaning validation protocol. Another option is to determine a "worst case" among the different active ingredients, and to only set limits for that worst-case active ingredient based on the lowest limit of any active ingredient in the group. Considerations for determining the worst-case active ingredient include difficulty of cleaning, solubility in the cleaning solution, and concentration of the active.

5.10 Bioburden Limits

In considering bioburden limits following cleaning, it is not expected that the cleaning process itself results in sterile equipment. If limits are established for bioburden in a cleaning validation protocol, those limits can be established using carryover calculations using the principles in **Sections 5.3** through **5.6.** For non-sterile manufacture, the starting point is an ARL in CFU/g or CFU/mL of the next manufactured product. The starting point for that ARL value is the bioburden specification of that next product. However, since there are sources of bioburden other than the cleaned equipment (e.g., from the raw materials of the next product), an adjustment factor is usually applied to the product specification to lower the bioburden ARL. These carryover calculations typically result in SAL values significantly above 10 CFU/cm^2 or a rinse sampling solution limit significantly above 100 CFU/mL. A risk assessment should be done to determine the acceptability of such values, including the nature of the next product (low water activity, which will not allow proliferation in the product vs. high water activity which, without preservatives, will allow proliferation in the next product). The acceptable bioburden level should also take into consideration effects on bioburden proliferation during the clean hold time. For this reason, many companies will establish very conservative bioburden limits, such as 1-2 CFU/cm^2 for surface sampling methods and the typical purified water limit of 100 CFU/mL for rinse samples.

However, even if the process equipment is steamed in place or autoclaved prior to manufacture of the next product, or even if the next product is sterile-filtered, it is typically the practice to evaluate bioburden to establish that the subsequent process is not overly challenged. Achievement of typical bioburden limits for non-sterile manufacturing (1-2 CFU/cm^2) is considered more than adequate for surface sampling. For rinse sampling that is performed with WFI, one approach is to utilize typical WFI values (10 CFU/100 mL), while another approach is to utilize a value of either 100 CFU/100 mL or 1,000 CFU/100 mL. The rationale for the higher limit is that the equipment will be subsequently steamed. Furthermore the WFI value is the value for the WFI in the recirculating loop; once it is removed from that loop and passed through clean equipment, there is not *necessarily* an expectation that it will still meet the WFI value.

An additional consideration for bioburden evaluation is the determination of objectionable organisms. Objectionable organisms are not necessarily limited to the USP specified organisms, but include organisms selected based on an understanding of the product and manufacturing situation. What makes an organism objectionable is not just the species, but also the number. The degree of identification may be identification down to the species level, or it may just include methods to exclude objectionable organisms. Furthermore, one approach is to identify all colonies that are found, while another approach is to only identify colonies if the number is above a certain threshold (e.g., 50% of the acceptance limit).

5.11 Endotoxin Limits

Endotoxin carryover to the final product is a concern for any product with endotoxin specifications. In this situation, it is common practice to measure endotoxin in the final rinse water, with limits typically set at the WFI limit of 0.25 EU/mL. If the equipment is depyrogenated by heat, endotoxin will be deactivated and measurement of endotoxin for cleaned equipment may not be required.

5.12 Visually Clean Criterion

Visual appearance of production surfaces is a direct measurement that verifies removal of residuals. The most common use of a visually clean criterion is to supplement swab and/or rinse testing for residues for cleaning validation protocols. In such cases, it is common practice *not* to establish a quantitative visual limit.

If visual examination is used *without* swab and rinse sampling, it is *required* to establish a *quantitative visual limit* for a residue on a specified surface under specified viewing conditions. If visual examination supplements swab and/or rinse sampling, such a visual limit determination *may* be done to further refine and/or limit what visually clean means. A discussion of that methodology for establishing a visual limit is given in **Section 7.7.3.** Provided the quantitative visual limit is *more stringent* than a SAL carryover limit (see **Section 5.5**) and provided that the equipment surfaces can be viewed in the cleaning validation protocol under conditions that are the same or more stringent than the viewing conditions established for the quantitative limit, then this visually clean criterion may be used without swab or rinse sampling. If this approach is used, a second-person verification in protocol execution should be utilized. Typical visual limits reported in the literature are 1-4 μg/cm^2. However, it should be recognized that this limit depends on factors or conditions such as the nature of the residue, the nature of the surface, the lighting, the distance of viewing, the angle of viewing, and the visual acuity of the operator.

The requirement for "visual cleanness" usually applies to equipment surfaces. It is not necessarily a requirement that swabs be visually clean after a surface is swabbed, due to the fact that residue which is not visible on a larger surface may become "visible" when concentrated on the smaller area of the swab head.

6.0 Sampling

In order to evaluate cleaning effectiveness, it is necessary to sample the surfaces of the equipment to establish the level of residuals present. It is essential for a cleaning validation program that the *appropriate* sampling methods are utilized. This section discusses issues that might be addressed in determining the appropriateness of types of sampling methods, sampling recovery validation studies, and training and qualification of samplers.

6.1 Sampling Method Selection

Selection of a sampling method depends on the nature of the equipment, the nature of the residue being measured, the residue limit, and the desired analytical method. Sampling methods discussed here are:

- Direct surface sampling
- Rinse sampling
- Swabbing
- Placebo sampling.

It should be noted that while regulatory documents refer to swabbing as "direct" sampling and to rinse sampling as "indirect" sampling, it is operationally more descriptive to refer to those sampling methods as "swab sampling" and "rinse sampling," and reserve the term "direct sampling" for techniques such as visual inspection.

Swab/wipe sampling, rinse sampling, and visual examination are listed as acceptable sampling techniques in most regulatory documents ***(20, 21, 22)***. Each method has its advantages and limitations. In a given protocol, multiple sampling methods may be used, such as "both rinse sampling and visual examination" or "rinse sampling, swab sampling, and visual examination," as required to adequately determine that the equipment is acceptably clean.

6.1.1 Direct Sampling Methods

Direct sampling methods (*as used in this document*) include both instrumental methods and visual inspection. It should be recognized that direct surface sampling incorporates elements of both sampling and analytical methods.

6.1.1.1 Visual Inspection

It is a well-accepted practice that a cleaning process should remove visible residues from the production equipment surfaces. The visual inspection of equipment has limitations in that some equipment surfaces (e.g., piping) are usually not accessible for viewing. The use of optical equipment like mirrors or endoscopes, as well as the use of additional lighting, can help to facilitate visual inspection. Ordinarily surfaces that are visually examined should be dry, as this represents a worst-case condition for visual inspection.

Remote inspection techniques (e.g., with fiber-optic probes and a viewing screen) are utilized when visual inspection by a trained inspector is difficult to perform. Things that might make visual inspection difficult include issues related to tank entry, the hazards of a potential residue, or inaccessibility of critical equipment surfaces. Additionally, one might use remote inspection techniques to supplement an "unaided" visual inspection procedure.

Borescopes, Fiberscopes, and Videoscopes allow visual inspection of hard-to-reach areas. Borescopes have been used to view the interior of piping and tank welds. A benefit of these scopes is that they typically can fit into confined spaces not accessible to operators. They are typically very maneuverable,

have additional lighting attached, and may come with optional magnification and/or zooming capabilities. The major drawbacks of these scopes are the difficulty of use, controlling lighting/brightness, and that the operator still has to make the determination if the area viewed is visually clean.

A Remote Visual Camera allows operators to view remote areas on a screen. The camera has most of the same strengths and weaknesses as the scopes, but the added benefit that operators can typically also record video or take pictures. Multiple operators can, at the same time, view what is on the screen. The potential to record video and allow multiple operators to view the screen may help support a site's visual inspection training program. Pictures printed from the camera may distort the actual amount of residue present since operators will typically zoom in on a particular area when taking a picture.

It should be noted that the basic regulatory expectation is that the equipment be visually clean by viewing with the *unaided* eye. Use of aids to magnify or otherwise improve visibility of residues should be seen as a more stringent use of visual examination.

6.1.1.2 Instrumental Methods

Instrumental methods typically involve a surface probe connected to an analytical instrument by a fiber-optic cable. For example, this may involve an attenuated total reflection probe connected to an FTIR instrument by a fiber-optic cable. The advantage of this type of sampling is that it is not necessary (as in swab and rinse sampling) to remove the residue from the surface for analysis. It also therefore does not require a separate sampling recovery study. The main disadvantages of this technique are limited length of the fiber-optic probe and the requirement that surfaces be relatively flat (therefore, many worst-case locations may not be sampled by this technique).

6.1.2 Rinse Sampling

Rinse sampling involves sampling the equipment by flowing solvent (which may be water, an aqueous solution, an organic solvent, or a water/organic solvent mixture) over all relevant equipment surfaces to remove residues, which are then measured in the rinse solvent. Collection of rinse samples should consider solubility, location, timing and volume. One type of rinse sampling technique is to take a "grab" sample from the final portion of the rinse solvent during the final rinse of the cleaning process. A "grab" sample is a single sample collected from a rinse solution that represents the composition of the rinse solution at that time. As used in this document, a grab sample generally refers to a single sample withdrawn from the final portion of a CIP rinse.

A second type of rinse sampling is to utilize a separate sampling rinse after completion of the process rinse. This separate sampling rinse may involve filling the equipment to an appropriate level with solvent and agitating that solvent to make the composition of the residue in the sampling rinse is homogeneous. Then a sample of that solvent is taken and analysed. This separate sampling rinse may alternatively be a separate CIP sampling rinse, which may involve a once-through sampling rinse or a recirculating sampling rinse. For a once-through separate sampling rinse, it is necessary to collect the entire volume of the separate sampling rinse, agitate it until it is homogeneous, and analyze a sample from the homogenous rinse. For a recirculating separate rinse, homogeneity is generally achieved by recirculation.

Advantages and disadvantages of both methods for rinse sampling are shown in **Table 6.1.2-1.**

Table 6.1.2-1 Comparison of Grab Sampling versus Separate Sampling Rinse

	"Grab" Sampling from Final Process Rinse	Separate Sampling Rinse
Advantages	• Represents the normal cleaning process • Requires no additional amounts of rinse solvent • Equipment can be used for further processing without additional steps	• Results can easily be used for carryover calculations • Represents what is left on surfaces after completion of cleaning process • More likely to result in an acceptable result if done correctly • Recirculating rinse likely to provide higher recovery • Allows use of a sampling solution other than the process rinse
Disadvantages	• Sample represents a worst case carryover to the next batch in that it reflects residue in the final rinse, not residue on surfaces after completion of the final rinse (but can demonstrate robustness of cleaning process) • Need to make assumptions about sampling for carryover calculations	• Utilizes an additional step • Require additional amount of rinse solvent • Possible contamination due to method of rinse solvent addition

Advantages and disadvantages of rinse sampling are given in **Table 6.1.2-2.**

Table 6.1.2-2 Advantages and Limitations of Rinse Sampling

Advantages	Limitations
• During rinsing, the entire product-containing surface is wetted. One analysis result represents the sum of all removed residues for the flow path. • The sampling procedure may not contaminate the equipment if process solvent is used. • Re-cleaning may not be required after sampling. • This method allows for conclusions on the cleanliness of areas that are not accessible for swabbing. • Adaptable to on-line analysis. • Less technique dependent. • Applicable for actives, cleaning agents, and bioburden. • Allows sampling of unique (e.g., porous) surfaces such as membranes and resins. • Useful for cleaning process design/development.	• Only residues soluble in rinse solvent can be detected. • Must assure that rinse sampling solution contacts all surfaces to adequately measure residues. • Does not deal with residues that preferentially transfer from one part of the equipment to the next product. • May dilute out the residue to be undetectable by the analytical method. • Limited information about location of areas that contributed to residues. • Knowing the rinse volume is critical to ensure accurate interpretation of results. • Usually limited to rinsing an entire piece of equipment, such as a vessel (except for extraction sampling). • Accessibility or presence of sampling ports for legacy equipment may be problematic.

Rationales for the use of rinse sampling include the following:

- Equipment not accessible for other types of sampling
- The residue is volatile, so measuring it on dried surfaces is not appropriate
- Rinse sampling adequately measures residues on surfaces.

6.1.2.1 Extraction Rinse Sampling for Small Parts

One special case of rinse sampling is sampling of small parts. Those parts may be sampled by swabbing but there are two options for rinse sampling. One type of rinse sampling is extraction from small parts. In an extraction procedure, the extraction solvent is placed in a clean vessel large enough to hold the sampled part. The small part is then placed in the extraction solution and agitated or sonicated for a fixed time. The sampling solution is then analyzed for potential residues. A second type of rinse sampling for small parts is typically used for items with an orifice, such as filling needles. In this procedure, a fixed volume of sampling solution is passed through the lumen and collected in a clean collection vessel. The sampling solution is agitated for uniformity, and then analyzed for the potential residues. Because the surface area and sampling volume are precisely known, limits can be accurately calculated for such situations.

6.1.2.2 Solvent Reflux Sampling

A second special case of rinse sampling is organic solvent reflux sampling. In this process, volatile organic solvent is added to the reactor of a manufacturing vessel. The solvent is heated to vaporize it. The solvent vapors condense on various upper parts of the manufacturing equipment, dissolve any soluble residues and carry it back to the reactor. While the technique for distribution of the solvent to the surfaces for sampling is different, the principles of rinse sampling are still present.

6.1.3 Swab and Wipe Sampling

Both swab sampling and wipe sampling involve wiping a surface with a fibrous material (most commonly). During the wiping procedure, the residue on the surface may be transferred to the fibrous material. The fibrous material is then placed in a solvent to transfer the residue to the solvent. The solvent is then analyzed for the residue by an appropriate and validated analytical method. For swabs, the fibrous material is some kind of textile (knitted, woven or nonwoven) attached to a plastic handle. Wipes are fibrous materials, usually woven or non-woven textiles, which are applied to the sampled surface by hand. A special case of swabs is the use of cotton balls or pads, which are moved across a surface with forceps. The selection of swab or wipes to be used requires an evaluation of the swab properties, such as extractables and shedding properties. Recovery of residues from surfaces also depends on the size and shape of the swab head or wipe, as well as the properties (such as flexibility and length) of the swab handle.

In most cases, the swabs and wipes are wetted with a solvent prior to sampling the surface. The solvent selected should be able to assist in dissolving the residue and also be compatible with the analytical method. For example, for HPLC analysis, the solvent could be mobile phase. For TOC and conductivity, the solvent is almost always water. For sampling the same site, companies may choose to sample the same surface area with multiple swabs or wipes in order to provide a higher percent recovery of residue from the surface. In such cases, the additional swab(s) or wipe(s) utilized may be either dry or wetted with the same solvent.

Wipes are typically larger pieces of textile material, and may be used to sample larger equipment areas.

The swab or wipe that has been applied to the surface is then extracted with a suitable solvent to

remove the analyte from the swab into the extraction solvent for analysis (see **Table 6.1.3-1** for advantages and limitations). The extraction solvent may be the same or different solvent as that used for wetting the swab.

Table 6.1.3-1 Advantages and Limitations of Swab/Wipe Sampling

Advantages	Limitations
• Enables the analysis of residues found on the specific surfaces. • Allows for sampling of areas that are more difficult to clean (i.e., worst cases). • Allows both dissolution and physical removal of residues. • Adaptable to a wide variety of surfaces • Economical and widely available. • Allows sampling of a defined area. • Applicable to active, microbial, and cleaning agent residues. • Small extraction volumes may provide for greater detectability.	• Only discrete sampling areas can be analysed to represent the entire equipment – sampling must include worst case locations. • The sampling itself can potentially contaminate (from fibers or solvent) the equipment. Re-cleaning may be required after sampling. • Some areas are not accessible for swabbing (e.g., piping systems). • Results may be technique dependent (such as surface area sampled). • Results may be location dependent (such as difficult to access surfaces) • Swab material and design may inhibit recovery and specificity of the method

6.2 Placebo Sampling

Placebo sampling can be used to detect residues on equipment through the processing of a placebo batch subsequent to the cleaning process. Placebo sampling is 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. Placebo sampling may present analytical challenges for measuring residues in a true placebo. Placebo sampling may also be called "mock runs" or "blank runs", which in biotechnology generally involves processing only with water. This latter concept is different from rinse sampling, in that the water is processed through the equipment much as the product would be processed.

In this sampling process, the equipment is first cleaned. Following cleaning, a manufacturing process is performed (to the extent feasible) using only a placebo product. Following processing, the placebo product is evaluated for residues as for any other cleaning validation sample as measures of possible contamination of a manufactured product with those residues. Placebo runs can be performed to demonstrate *actual* carryover to the processed material, but if done, are typically done to complement swab/wipe and/or rinse sampling.

6.3 Sampling for Microbial and Endotoxin Analysis

Sampling for bioburden may involve rinse-water sampling and/or swabbing, but may also involve contact plates. Consideration should be given to the sampling solution for swabbing and rinsing. For swabbing, a sterile solution, such as phosphate-buffered saline, should be used. For rinse sampling, it is generally not practical to sample large equipment items with sterile water; however, for extraction of small parts, the use of sterile water or a sterile solution is preferred. For large equipment, rinse sampling is generally done with purified water or WFI, and results may be compared to a blank taken from the same use point. Rinse-water sampling for bioburden should involve use of sterile sample

containers. "Aseptic" sampling technique, much like is used for cleanroom bioburden sampling, is required for any microbial method to avoid external contamination of the sample.

Sampling for endotoxin is almost always a rinse water sample, preferably with low endotoxin water.

6.4 Additional Considerations

It is preferred to have a separate sampling SOP (apart from any special instructions in a cleaning validation protocol). This helps prevent "procedure drift", which might occur if the swabbing procedure text is just repeated in every protocol. It also helps insure that the same sampling procedure is used in recovery studies as in protocol execution, and thus simplifies training. The rinse sampling procedure may be the same procedure that is used for sampling water systems, appropriately modified to cover sampling of process equipment.

In selecting sampling techniques, considerations should be given to the compatibility of the sampling materials (such as vials, swabs, sampling solutions) with each other, with the nature of the residue, and the nature of the analytical method. Furthermore, any requirement for cleaning or removing sampling materials from the sampled surface in a cleaning validation protocol should be addressed in the design/selection of sampling methods, materials, and parameters.

Finally, in taking samples in a protocol, consideration should be given to the impact of a given sample on subsequent samples. This includes the order in which samples are taken. This "order" includes consideration of the type of sampling method (e.g., visual, rinse, swab) as well as the type of residue (e.g., active, cleaning agent, bioburden, endotoxin).

6.5 Sampling Recovery Studies

Sampling recovery studies are generally required to adequately demonstrate that a residue, if present on equipment surfaces, can be adequately measured or quantified by the combination of the analytical method and the sampling procedure. These studies provide a scientific basis for utilizing those sampling and analytical methods to measure residues. The objective should be to establish a reproducible level of recovery from the equipment surfaces. Three types of sampling recoveries are discussed below: swab sampling recovery, rinse sampling recovery and "visual examination" recovery. For swab and rinse sampling, recovery studies may be performed as part of the analytical method validation or they may be performed as separate studies once it is determined that the analytical method can appropriately measure residues in solutions. Sampling recovery studies are laboratory studies involving coupons of sampled equipment of different materials of construction (such as stainless steel, glass, PTFE, and EPDM) spiked with residues to be measured.

6.5.1 General Considerations

Recovery studies *may* not be required for certain residues that are known to be readily soluble (e.g., as defined in the USP or Merck Index and used well below the solubility limit (such as sodium hydroxide or phosphoric acid used as cleaning agents), provided the residues are not reactive with or absorbed into the surface.

In performing recovery studies for swabbing and rinse sampling, the amount of material spiked onto coupons should represent an amount equal to what could be present at the residue limit. If additional levels are spiked, levels should represent levels of actual values present in cleaning validation protocols. It should be recognized that spiked levels at extremely low levels may give lower recovery percentages due to the inherent variability of the analytical method at those low levels.

The spiked residue should represent the same residue present at the end of the cleaning process. In actual fact, the residues present at the end of cleaning may include a combination of active ingredient, cleaning agent, excipient, and/or degradation products. It is common practice, however, to only spike the active ingredient when doing recovery studies for the active ingredient, and to only spike with cleaning agent when doing recovery studies for cleaning agent. Spiking of the active ingredient in its final formulation may be considered when spiking of the active ingredient alone is not practical. Finally, drying and/or holding times of spiked coupons should be appropriate for the nature of the residue.

If the active degrades during the cleaning process, it is common practice to perform recovery studies by spiking with the active ingredient itself, unless there is information that indicates the degradation products may have a significantly different recovery level from the active ingredient itself. Furthermore, if the degradation product has unusual safety or solubility concerns, recovery studies by spiking directly with that degradant should be considered. Because of possible concerns about degradation of the active ingredient after completion of the cleaning process, but before sampling, that maximum time interval between spiking and sampling should be considered in performing recovery studies.

Recovery values should be established for all surfaces sampled. For swab and rinse sampling, one approach for this is to perform recovery studies on all surfaces. An alternative is to perform one residue study on a surface which through documented evidence is equivalent (in terms of percent recovery) to other surfaces for which a formal recovery study is not performed. This is essentially a grouping or family approach for recovery studies. Equivalence for establishing the group or family may be established based on published studies or in-house data. Another approach is to exclude formal recovery studies for sampled surfaces constituting less than a small percentage (such as 1% or 2%) of the total equipment surface area; in such cases, the recovery value used for that excluded surface is the lowest recovery of any other surface type for which a formal sampling recovery study was performed, or the minimum acceptable recovery percentage required by the company's procedures.

6.5.2 Swab/Wipe Recovery

For this section, the term swab or swabbing is used; however, descriptions for swab recovery studies also apply to wipe sampling, except as noted. For swab recovery studies, coupons are spiked in a controlled manner with solutions of the sampled residue, allowed to dry, and sampled with the swabbing procedure to be utilized in the cleaning validation protocol. The swab is extracted in a suitable solvent and the amount of residue measured in that solvent sample. The amount recovered is compared to the amount spiked on the coupon and the result is expressed as percent recovery. Because swabbing is a manual procedure, typically each person performs a recovery study with three replicates. It is preferable to have at least two people perform swabbing recovery studies for each combination of residue and surface type. The recovery percentage established by the study may be defined in different ways, but typically is defined as the lowest average recovery of any one swab operator. An acceptable swab recovery depends on how that swab recovery is being used. If the recovery is performed to qualify the sampling method *without correction* of either a limit or an analytical result then a recovery percentage such as 70% or more is typically required. If the recovery percentage is *used to correct* a residue limit *or* an analytical result then a recovery of 50% or more is typically required. An upper limit for percent recovery should be established to deal with studies where the measured recovery is greater than 100%. Recoveries of less than 50% typically require a written rationale of why that percentage is appropriate.

As part of the swab method development, spiking of residue directly onto the swab head to determine recovery (release) from the swab head material may be done. Such a study should also be considered if recovery levels from spiking of surfaces is unacceptable, and it is desired to find the cause of the low recovery.

At a minimum, recovery values are generally performed at the residue limit on the surface (e.g., in $\mu g/cm^2$). While it is possible to perform recoveries at different spiked levels, in general there is little value to such additional spiked levels because of the variability of the sampling procedure. It is preferable to perform additional replicates at the one residue limit rather than studies at additional levels. Acceptable variation for recovery results at one spiked level is typically on the order of 15-30% RSD. If recovery studies are done by more than one swab operator, it is also appropriate to have a criterion for determining acceptable variation between operators. Examples of criteria used include variation of no more than a maximum amount between average percentage values, or variation of no more than a maximum relative percentage between average percentage values. Use of statistical tests for significance is generally not necessary for such determinations.

Swab recovery studies are typically performed on a nominal coupon surface area using the same area as is swabbed during sampling for protocol execution. This area is typically either 25 cm^2 or 100 cm^2 while wiping studies are done on larger areas. In sampling manufacturing equipment for a protocol, it is not always possible to swab a 10 cm X 10 cm area (it might be necessary to swab a 5 cm X 20 cm area). Furthermore, it might not be practical to swab exactly 100 cm^2 (an area of 60 cm^2 or 128 cm^2 may be required because of the specific equipment geometry). In such cases, the recovery percentage based on sampling 10 cm X 10 cm may be applied to each of those cases. If such an approach is used, a range of acceptable surface area (such 25% to 150% of the nominal sampled area) should be established. However, if the sampled area for equipment surfaces in a protocol varies from the nominal value, the residue limit for that sample should be adjusted based on the actual surface area swabbed.

6.5.3 Rinse Recovery

Rinse recovery studies address the validity of rinse sampling for that residue. They demonstrate that if the residue were on a surface, that residue would be effectively removed and could be analyzed in the rinse solution. Rinse recovery studies address the U.S. FDA's "dirty pot" and "baby/bath water" analogies ***(20)***. Rinse recovery studies, like swab recovery studies, can be performed on coupons that have been spiked with solutions of the target residue and then allowed to dry. For swab recoveries, it is necessary to perform the exact swabbing procedure to be used in the cleaning validation protocol. For rinse sampling, in contrast, the exact rinsing procedure (except for the special case of extraction sampling) cannot be *duplicated* in the laboratory. However, it is possible to *simulate* the rinsing procedure in the laboratory. Where possible, the conditions of the simulated rinse should be the same as the equipment rinsing situation. This includes selection of rinsing solvent as well as the temperature of the rinsing solvent. In other cases, the rinsing conditions should be selected as the same or a worst case as compared to the equipment rinsing situation. For example, the ratio of solvent to sampled surface area should be the same or lower in the recovery study as compared to the equipment rinsing situation.

One method of simulating the rinse process is to suspend a spiked coupon above a clean collection vessel, and cascade rinse solution across the surface into the collection vessel. Another method is to spike the bottom of a beaker of the appropriate material of construction, allow the residue to dry, add rinse solution to the beaker and apply gentle agitation for a time which approximates the time of the final rinse. The rinse solution is either pipetted or decanted from the beaker and analyzed. A third option, used in cases where a beaker of suitable material of construction is not available, is to place a spiked coupon in the bottom of a beaker and perform a simulated rinse as in the second method.

Since laboratory rinse sampling studies are generally not operator dependent, three replicates by one operator may be adequate to determine the percent recovery. Acceptable percent recoveries are typically established at the same levels and conditions as for swab recovery studies.

6.5.4 "Recovery" in Visual Inspection

This process is actually the determination of a quantitative "visual detection limit". If visual examination is used to supplement swab or rinse sampling, such determination of a visual detection limit may be done but is not required. A visual detection limit under specified viewing conditions can be determined by spiking coupons of the equipment surface materials with solutions of the residue at different levels (in $\mu g/cm^2$), and having a panel of trained observers determine the lowest level at which residues are clearly visible across the spiked surface. The significance of such a visual detection limit is that if equipment surfaces are determined to be visually clean under the same (or more stringent) viewing conditions in a cleaning validation protocol, the level of the residue is below the visual detection limit. Appropriate viewing conditions include distance, lighting and angle. The visual limit depends on the nature of the residue as well as the nature of the surface (e.g., stainless steel vs. PTFE) and the visual acuity of the inspector. Typical values reported in the literature for a visual detection limit are 1-4 $\mu g/cm^2$ ***(23)***. For this determination, a percent recovery is not established; the purpose is to establish a value where residues are clearly visible so that any surface observed as visually clean is clearly below that value.

6.5.5 Recovery for Bioburden and Endotoxin Sampling

Recovery studies to determine percentage recovery *from surfaces* are not appropriate and are not normally done for microbiological sampling. One reason for this is the question of enumeration in microbiological tests – "colony forming units" are typically counted as opposed to individual organisms. A second reason for this is that vegetative organisms will die or lose viability when dried on a coupon in a standard sampling recovery procedure. A third reason is that it is unclear which species should be used for a recovery study. A fourth reason is that typically the limits set for bioburden are significantly below what could possibly cause either product quality issues or process performance (e.g., SIP) issues; therefore, even though recovery may be low (<50%), product quality and/or process performance is not impacted by not including a recovery factor.

Endotoxin recovery studies from surfaces using the sampling method are not ordinarily performed. One reason is related to the low levels that are typically present on cleaned surfaces. Additionally, only standard endotoxin from LAL test kit suppliers can be used for recovery studies and these may not be indicative regarding detection and/or removal of endogenic endotoxins present from a manufacturing process. Finally, the largest quantity of endotoxin present in a manufacturing vessel typically is endotoxin within a soil matrix. The cleaning process itself is very effective in physically removing this endotoxin along with other manufacturing soils.

6.6 Training and Qualification of Samplers

Training involves the steps taken to assist the prospective sampler in learning the technique of sampling/inspection. For purposes of this section, "sampling" and "sampler" also include "inspection" and "inspector" for visual evaluation. Qualification involves the process of "certifying" that the prospective sampler can appropriately sample.

Training always precedes qualification. At a minimum, *training* involves reading of the sampling procedure and demonstrating the correct procedure by a trained sampler. During the reading and demonstration, the trained sampler provides commentary on the rationale for certain practices or aspects of the sampling procedure. Demonstration of technique may also utilize a visual indicator on the swabbed surface which assists the trainee in seeing consequences of poor technique. The last step in training is demonstration of the correct procedure by the prospective sampler.

Qualification processes used for sampling will depend on the type of sampling performed. Qualification may involve merely demonstration of correct technique (that is, the last step of the training process), or it may involve a "test" that challenges the trainee's ability to perform the activity correctly (e.g., perform visual inspection using an array of coupons where some are soiled and others are not or perform swab sampling for a known soil residue level on coupons). Either type of qualification may be repeated on a regular basis or upon any retraining of a sampler. Retraining may be conducted based on suspected operator error in a swabbing process, or it may be done because an operator has not performed a swabbing event over a certain time frame.

6.6.1 Key Issues for Training for Swab Sampling

Note that what is written in this section about swab sampling applies appropriately to wipe sampling.

Four keys to consistency in swab sampling training are emphasis on consistency of wetting the swab head, consistency of the swabbing motion (including overlapping strokes), consistency in applied pressure, and consistency in swabbing of the correct surface area. It is assumed, of course, that the correct swab, the correct number of swabs, and the correct wetting solution (if any) for the swab are utilized. A fifth factor for some types of swab sampling (such as sampling involving TOC analysis) is the emphasis on preventing external contamination of the swab, such as from the presence of volatile organics in the atmosphere around the sampling location.

Since swab sampling is not unlike manual cleaning processes in that it depends on a person for a high degree for consistency, consideration should be given to have swab samplers retrained and/or requalified on an established basis. Retraining may involve the same process as for initial training or may involve only portions of that initial training. Requalification generally involves a repeat of the initial qualification process. The need for retraining and/or requalification should also be addressed as part of change control for the swabbing procedure as well as when swab sampling "operator error" is suspected in the investigation of a nonconforming result.

6.6.2 Key Issues for Training for Rinse Sampling

The major concern for accuracy in rinse samples is to prevent contamination of the rinse sample. This contamination may come from for example, the sampling port, environment around the sampling port, and/or the operator. Steps to prevent contamination may include adequately flushing or cleaning the port prior to taking a sample, as well as avoiding sample contamination due to the use of isopropanol on gloves or use of isopropanol to clean the port (prior to sampling) if TOC is the analytical procedure. In training rinse samplers to take a grab sample for the final rinse of a CIP cycle, timing of the sampling process is critical. Typically, the very last portion of the rinse is sampled but it may be acceptable to sample before that time if such sampling represents a worst case. However, once process rinsing is complete, there is no way to go back and collect a rinse sample (unless a separate sampling rinse is performed).

Since the consistency of rinse sampling is less operator dependent, there may be no need for routine retraining and/or requalification of operators; however, the need for retraining and requalification should also be addressed as part of change control for the rinse sampling procedure as well as when rinse sampling "operator error" is suspected in the investigation of a nonconforming result.

6.6.3 Training for Visual Inspection

Training for visual inspection depends on whether the visual inspection is part of a protocol execution, routine monitoring, or laboratory "limit of detection" determination. In any case, it is preferred to have a visual inspection SOP so that training can be for that SOP. Visual acuity of visual inspectors for either type of visual examination should be addressed.

For training of visual inspectors in a *protocol execution*, key issues are access to sites for viewing, appropriate lighting, and the ability to discern the difference between residues on the surface and surface imperfections. An important element of visual inspection training is to know when to call for further analysis to determine the nature of the residue. For example, if what appears to be rouge is seen on the equipment, the presence of that residue should be noted. Determining whether that residue causes a failure in the cleaning process is a *separate* decision.

The procedure for visual inspection for laboratory "limit of detection" determination is generally different from that of visual inspection during protocol execution because the objective is different. The objective is to determine at what level a certain residue can be consistently seen across a spiked surface in order to correlate a visual detectability limit with a level of known residue(s) below that spiked level. This procedure may be in a separate SOP or may be incorporated in an overall SOP for visual inspection. In addition to the same elements that are included in training for protocol execution, a key consideration for training in this procedure, which involves viewing spiked coupons, is a careful distinction between a visually clean surface, a partially soiled surface (in which residue is apparent only over a portion of the spiked area), and a "fully" soiled surface. Furthermore, the determination of a "visual limit" in the laboratory should be done under conditions similar (or worst case) as compared to visual examination of equipment in a protocol. This includes considerations of lighting, distance, and angle of viewing.

7.0 Analytical Methods

It is essential to a cleaning validation program that the appropriate analytical methods are utilized. Analytical methods must be appropriate in that they can adequately detect and measure the residue(s) of concern. It is also important to understand what can be concluded from the analytical result (e.g., was the product or cleaning agent measured and were the results acceptable?). The results of testing will determine if the cleaning cycle is acceptable or needs improvement. This section discusses considerations in selecting the appropriate test methods, including information on the applicability and use of both chemical and microbial test methods, and test method validation.

The emphasis in this section will not be so much on describing the features and limitations of methods (although that will be done to a limited extent), as it will be on the *thought process* of deciding what information is obtained and when a certain analytical method will be useful. Cleaning process understanding is the key to selecting the appropriate analytical method for various stages of cleaning validation

7.1 Purposes of the Analytical Methods

In a lifecycle approach to cleaning validation, different analytical methods may be appropriate for evaluation of residues at the different stages of the cleaning validation lifecycle. The lifecycle stages of cleaning validation are design/development, qualification, and validation maintenance. Analytical methods may also be used as part of investigations during any lifecycle stage. It is important to consider and evaluate what information one wants to obtain and what information can be obtained from use of a given analytical procedure.

For example, in early development work, there may not be adequate information on the nature of residues (e.g., is the active ingredient degraded?) and a specific analytical method may not have been validated. However, nonspecific methods may give a reasonably accurate picture of the overall effectiveness of the cleaning process for cleaning process development, even though that nonspecific method may or may not be the analytical method chosen for the cleaning validation protocols.

Another example involves the selection of analytical methods for investigations. For the validation runs (qualification runs), it is usually preferred to have an analytical method that can appropriately determine whether the target residue (e.g., the active ingredient) is at or below the predetermined acceptance limit for that residue. But for an investigation into a deviation (nonconformance), in certain circumstances (such as with the use of a nonspecific method in a validation protocol) it may be more important for the investigation to have an analytical method that can qualitatively determine the nature of that residue (e.g., is it active ingredient, cleaning agent or excipient?).

It is important to emphasize that the thought process of *why* an analytical method is being used is critical for having a robust, science and risk-based approach to cleaning validation. Just because a method has been used in the past does not necessarily mean it will useful for a new application.

7.2 Practical Considerations in Selecting Analytical Methods

In an ideal world, the best method for a given task could be chosen; in the real world, selection of analytical methods may be limited by *practical* considerations. In many cases, it is important not that the analytical method be the *best* method available but that it be *adequate* for the intended purpose. In selecting analytical methods, one must consider readily available methodologies within a given company. For example, it is not likely that a company will invest in a new analytical method if existing methods are adequate for the intended purpose. New methods may mean capital equipment purchases, training of analysts and maintenance of the equipment; the related costs should be weighed against the expected benefits. For example, total organic carbon (TOC) was not widely considered for

cleaning validation until TOC replaced the readily oxidizable substances pharmacopeial method, after which pharmaceutical companies were readily familiar with and comfortable with the technology.

On the other hand, if a new analytical method is required because existing in-house methods are not adequate for the intended purpose, then that new method should be considered. These may be implemented by using contract analytical laboratories or by bringing the new analytical methodology in-house. A decision on bringing the method in-house versus using a contract laboratory may be based on business considerations.

7.3 Specific vs. Nonspecific Analytical Methods for Validation Protocols

Specific analytical methods are those which measure a certain residue in the presence of *expected* interferences. If the target analyte in a validation protocol is the active ingredient, such interferences may include degradation products and related substances, excipients, cleaning agents and cleaning process by-products. Examples of specific methods include liquid chromatography (including HPLC, UPLC and TLC) and spectrophotometry (including UV, visible and infrared). Each of these methods requires the use of an appropriate reference standard. In contrast, nonspecific analytical methods measure a general property, such as conductivity or TOC, which could be due to a *variety* of analytes or sources.

Selection of an analytical method may depend on the nature of the residue as it exists after the cleaning process. Only if an active ingredient is *not degraded* during the cleaning process (e.g., surviving high temperatures and pH extremes in an aqueous environment) does it make sense to use a specific analytical method for that active ingredient. If a specific analytical method for an active ingredient were utilized following a cleaning process that has been demonstrated to degrade that active ingredient, it is likely that residues of the active ingredient would be nondetectable (i.e. not measurable) by that specific analytical method. In such a case, use of a specific analytical method for the degradant or use of a nonspecific method (such as TOC) may be considered for measuring residues in a validation protocol. Alternatively, if limits are established for the degradation product of an active ingredient, then a specific analytical method for the degradant may be considered for use.

It should be recognized that the proper use of a nonspecific analytical method may provide a more robust demonstration of acceptable cleaning in a validation protocol, because it may have responses from species other than the target residue, yet those responses must be assumed as due to the target residue ***(24)***. However, exceeding the residue limit using a nonspecific analytical method provides no information on the nature of the failure. The high analytical result may be due to responses from the active ingredient, the excipients, the cleaning agent, and/or a combination of those species.

Nothing in this Technical Report should be interpreted as saying that, as a general principle, specific analytical methods should be used in preference to nonspecific analytical methods.

7.3.1 Regulatory Status of Specific and Nonspecific Methods

Both specific methods and nonspecific methods have been found acceptable by regulatory authorities. However, one must be careful not to misuse an analytical method. For example, specific methods can be misused by failing to recognize the degradation of the active ingredient in the cleaning process, and nonspecific methods can be misused by failing to attribute the nonspecific response entirely to the residue of concern.

The U.S. FDA cleaning validation guidance states that one should "Determine the specificity and

sensitivity of the analytical method used to detect residuals or contaminants" ***(20)***. While some have interpreted this to mean that a specific analytical method should be used, a better interpretation is that irrespective of the type of method selected, make sure it is used appropriately. The European PIC/S recommendations state that "The analytical methods used to detect residuals or contaminants should be specific for the substance to be assayed…." ***(22)***. This again has been interpreted to mean that only specific analytical methods should be used. However, it is not applied in that manner since nonspecific methods are widely used by companies worldwide and have been accepted by the U.S. FDA and European regulatory authorities.

7.4 Most Commonly Used Analytical Techniques

The focus of this section is to discuss the most commonly used analytical procedures in pharmaceutical cleaning validation ***(25)***. The Task Force believes it was more appropriate to focus on common uses of analytical methods, based on the stages of cleaning validation where they have been demonstrated to provide relevant information. The features, benefits and limitations of methods are often situational and are therefore not covered here.

Additional considerations in selecting methods are listed below:

- Availability of instrumentation
- Speed of analysis
- Specificity of technique
- Sampling limitations (including sampling solvents)
- Detection/quantitation limit
- Linearity of response
- Online adaptability
- Cost

Most applications in pharmaceutical cleaning validation involve quantitation of residues over a validated range. However, in certain situations, pass-fail tests, also known as "go-no go" testing, may be used to establish that the residue is below the acceptance limit. Such testing may be used in qualification runs for clinical manufacture (where the effort to fully validate an analytical method over a linear range may be costly) or for routine monitoring and equipment release based on final rinse solvent testing. A pass-fail test generally does not demonstrate the robustness of the cleaning process unless the pass-fail point is significantly below the desired acceptance limit. Since the transition point is a range, the range must be known and its relationship to the limits must be established in the validation process. The actual result, although passing, could have been very close to failure and with normal plus/minus variation it could actually represent a failed result.

For more information on analytical method use in biotechnology manufacture, please consult PDA Technical Report No. 49, *Points to Consider for Biotechnology Cleaning Validation* ***(2)***.

7.4.1 Liquid Chromatography (LC)

LC includes HPLC (High Performance Liquid Chromatography), UPLC (Ultra Performance Liquid Chromatography, and TLC (Thin Layer Chromatography). All these methods involve the separation of component by a chromatography procedure and then the measurement of one or more separated species. For HPLC and UPLC, the measurement is typically ultraviolet (UV) detectors, although other appropriate detectors may be used based on the analyte of interest.

HPLC and UPLC methods are typically specific methods, which are widely used for measurement of active ingredients in small molecule-manufacturing (both API and drug product manufacturing). In many cases, HPLC/UPLC methods have been previously developed as a potency assay method for the active ingredient, and only need minor modification to make the method suitable for use as a method for residue determination in qualification runs. Those additional modifications may involve

confirming that the useful range is suitable for residue determinations and that additional "expected interferences" that are present in the cleaning system do not interfere with measurement of the active ingredient. HPLC/UPLC methods may not be suitable for measuring residues of an active ingredient if the active ingredient is degraded in the cleaning process, unless the chromatography conditions allow separation and measurement of degradants of interest.

TLC methods may be used for various stages for cleaning of small molecules. For example it may be used for design/development to confirm and characterize degradation of the active. TLC methods may also be used for any investigation (at any stage of cleaning validation) to characterize residues.

7.4.2 UltraViolet/Visible Spectrophotometry (UV/Vis)

UV/Vis involves measuring transmission/absorbance of a specified wavelength of light by a solvent solution of the residue. It typically requires a chromophore in the molecule, although it is also possible to modify the residue to produce a chromophore. For example, it is commonly used in small-molecule manufacturing, particularly for API manufacturing where it is not necessary to separate it from a matrix to quantify the residue. Because of its simplicity, UV/Vis techniques may be used in the design/development, qualification and validation maintenance stages of cleaning validation as well as for any investigations. UV/Vis has also the possibility of being used in PAT applications for completion of the cleaning steps for small molecule API manufacturing ***(26)***.

7.4.3 Total Organic Carbon (TOC)

TOC is applicable to any residue containing significant amounts of organic carbon. The TOC method is based on oxidizing the carbon present and measuring the carbon dioxide produced. Oxidizing methods include UV, persulfate, and combustion. Techniques for measuring the generated carbon dioxide include conductivity, membrane-based conductivity and infrared. Both online and offline applications of TOC are possible.

For use of TOC, the target residue must have adequate aqueous solubility for the intended purpose. The most common way of applying the TOC method to a cleaning validation testing strategy is to assume that all residues detected are due to the target residue ***(24)***. In manufacturing situations, TOC is commonly used for measuring residues if the target residue (e.g., the active ingredient) is degraded during the cleaning process. However, it may also be used in situations where the active is not degraded. The rationale for use of TOC in such situations is ease of analytical method development and the worst-case assumptions inherent in TOC analysis.

TOC may be used for all stages of cleaning validation, including design/development, qualification and validation maintenance as well as for investigations.

7.4.4 Conductivity

Conductivity measurement is a method to detect dissociated ionic substances in water samples. For qualification protocols conductivity readings are expressed in micro-Siemens/cm (μS/cm); for control and monitoring of the cleaning solution, conductivity readings are expressed as milliSiemens/cm (mS/cm). It is often used to measure cleaning agent residues (e.g., caustic or acidic agents) and to control cleaning agent concentration in automated cleaning processes (e.g., CIP). Conductivity readings are highly influenced by the sample temperature. Temperature adjustment of the sample, automated temperature compensation or a conductivity/concentration curve at a specified temperature can be used to standardize the measurements.

To allow correlation of conductivity readings with concentrations of cleaning agent, a dilution curve

(conductivity vs. concentration) should be established (at a relevant temperature) by conductivity measurements of different dilutions in the relevant range near the acceptance value.

Conductivity is a nonspecific method that correlates linearly (within a defined range) to the ion concentration in an aqueous sample. Analytical instruments are robust and can be used on the manufacturing floor by trained personnel. The method cannot differentiate between different ions. Therefore, as with TOC, all conductivity results above the water baseline should be attributed to the contaminant in question (e.g., the cleaning agent).

Conductivity is often a function of alkaline or acidic cleaning agent. Measuring conductivity is a good measure of the completion of rinsing, and therefore an indirect measure of good cleaning for routine monitoring of a cleaning process.

Conductivity can also be used for measuring residues of an ionic active ingredient, either in cases where the cleaning agent is water alone or in other cases involving ionic cleaning agents if all the conductivity response is attributed to the active ingredient (even though some of the response may be due to the cleaning agent).

7.4.5 Organoleptic Evaluation

"Organoleptic" evaluation includes visual inspection as well as other evaluations such as smell. Visual inspection is commonly used during all stages of cleaning validation, as it is a minimum requirement under GMPs for use of equipment for manufacture. Visual inspection is a nonspecific method in that the nature of the residue generally cannot be identified except by further analysis.

Training and a detailed documented procedure is required to ensure that "visually clean" from one operator to the next is consistent. What one can visually see will vary with distance, angle, lighting, nature of surface, and inspector's visual acuity. Some equipment surfaces (e.g., piping) are usually not accessible for visual inspection. The use of optical equipment like mirrors, remote videoscopes, or borescopes can help to facilitate visual inspection.

The visual inspection procedure should specify how operators are to deal with visual observations. Visual inspection may find four different types of visual observations: residue, surface anomalies, foreign object and water. Residue is the *main* concern which would constitute a visual failure when one is assessing the acceptability of a cleaning cycle. A sample of the residue should be collected for further testing, if possible, to assist in the investigation of the cause. Typically, surface anomalies and foreign objects are not considered visual inspection failures for cleaning validation purposes, but must be further investigated and corrected, as applicable. Surface anomalies should be noted and a "suitability for use" assessment should be performed to remediate any issue(s) found. Rouge is the most common type of surface anomaly discovered during visual inspection; rouge is generally considered a preventive maintenance problem, not a cleaning process problem. Foreign objects and their removal should be documented. Also, how the foreign object came to be in the equipment should be investigated. Sometimes a distinction is made between absence of water pooling ("free drained equipment") and the absence of any visible water droplets ("dry equipment"). Particularly for water pooling, the observation should be documented, the cause investigated, and the impact on issues such as visual examination and bioburden proliferation on storage should be addressed.

All equipment surfaces should be visually inspected if possible. Visual inspection may not be performed on the interior of lines and tubing (although outlets may be inspected) on equipment where disassembly of the equipment is not practical or possible, or where inspection of the equipment could potentially be dangerous to the inspector (e.g., entry into a confined space).

A training program should be developed for visual inspection. Inspectors typically should be trained and/or requalified on an established basis. If visual inspection is not possible on an area of concern, it is important to ensure that other sampling methods (such as rinse sampling) can adequately detect potential residues of concern.

Smell as an organoleptic method is generally only used if an unusual smell occurs during sampling of the equipment, which would suggest the need for an investigation.

7.5 Other Useful Analytical Techniques

Below are other techniques which may be useful for various stages of cleaning validation.

7.5.1 pH

pH is a measure of the hydrogen ion concentration. It can be used as a monitoring process check, particularly when equipment is stored wet in a preservative solution (typically acid or base). pH can also be used to verify qualitatively the presence of the correct cleaning solution. pH can be used to complement conductivity measurements. However, pH is less useful than conductivity for measuring residues of alkaline or acidic cleaning solutions because pH has a logarithmic relation with hydrogen ion concentration, whereas conductivity has a direct, linear relationship with ions. Furthermore, there is not necessarily a direct correlation of conductivity and pH, particularly for neutralized cleaning agents.

7.5.2 InfraRed (IR)

This includes both FTIR (Fourier Transform InfraRed) and NIR (Near InfraRed). These techniques are most useful in an investigation where there is a need to identify organic residues that may be present. FTIR has also been combined with a fiber-optic probe for direct quantitative measurement of residues on surfaces for qualification protocols *(27)*.

7.5.3 Light Microscopy

Light microscopy, including Scanning Electron Microscopy (SEM), is a method of identifying contaminants on equipment surfaces. In many cases, conventional light microscopy and SEM can be combined with other analytical techniques, such as x-ray diffraction, mass spectrometry, and nuclear magnetic resonance (NMR). Microscopic techniques alone may identify the physical nature of a residue but not the chemical nature. One of the practical applications of microscopy is in the evaluation and identification of unknown contaminants on new or used equipment. These techniques are especially valuable in the evaluation of residues in an investigation.

7.5.4 Titrations

Titration is another simple analytical method that is often overlooked even though it might provide valuable information in the proper cleaning situation. Titrations may be specific (orthophosphate ions) or nonspecific (e.g., for all anionic surfactants). This method is more likely to be used for alkaline or acidic cleaning agent analysis in qualification runs.

7.5.5 Gravimetric Analysis

Gravimetric analysis can be useful for design/development studies and for qualification runs. It is most commonly used for determining residues in small-molecule API synthesis where a larger volume of a solvent rinse or solvent reflux is evaporated to dryness.

7.5.6 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. Its use is generally limited to biotechnology and biologics manufacture where it can be used in the design/development stage to confirm degradation of the active ingredient and in any investigations.

7.5.7 Capillary Zone Electrophoresis (CZE)

Also known as capillary electrophoresis (CE), this technique separates residues by charge and frictional forces in an electrical field. Detection is usually with a fluorescence detector. CZE has been applied mostly in the biotechnology industry for active ingredients and degraded active ingredients where it can be used in design/development and qualification stages as well as in investigations.

7.5.8 Atomic Absorption (AA) and Inductively Coupled Plasma (ICP)

Both of these techniques can be used for measuring metals in solution, where the metal is part of a formulation or for unknown residues, such as suspected rouge.

7.5.9 Ion Mobility Spectrometry (IMS)

This technique is a type of mass spectrometry which only provides information on the time of flight of the analyzed species. It has been promoted for its short analysis time (a few minutes). It may have more application for routine monitoring and release.

7.6 Microbial Test Methods

The 1993 U.S. FDA cleaning validation guidance states that "Control of the bioburden through adequate cleaning and storage of equipment is important to ensure that subsequent sterilization or sanitization procedures achieve the necessary assurance of sterility" ***(20)***. The PIC/S recommendations call for "the validation of cleaning procedures for the removal of contaminants associated with the previous products, residues of cleaning agents as well as the control of potential microbial contaminants" ***(22)***. Control of microbial residues is thus an important part of cleaning validation. Microbial residues include bioburden and endotoxin. Typically bioburden sampling and analysis is performed during cleaning validation protocols unless there is a documented science- and risk-rationale for omitting such sampling and analysis. Science- and risk-based rationales for excluding microbiological testing in protocols may include manufacturing considerations, such as all solvent processing for small-molecule API manufacture, use of a final alcohol rinse for oral dose drug products, use of subsequent sterilization cycles, and/or demonstration of adequate microbial control in sufficiently similar cleaning processes.

7.6.1 Endotoxin

Typically, endotoxin testing is performed for cleaning validation runs if the next product has endotoxin specifications. Endotoxin analytical methods are typically compendial methods. Science- and risk-based rationales for excluding endotoxin testing in protocols may include manufacturing considerations, such as all solvent processing for small-molecule API manufacture, use of a validated endotoxin reduction step, and/or demonstration of adequate endotoxin control in sufficiently similar cleaning processes.

7.6.2 Bioburden

Testing of bioburden is done through rinse-water sampling, swab sampling and contact plate sam-

pling. Rinse-water sampling typically involves membrane filtration, placement of the membrane on an appropriate agar, incubation, and a count of CFUs. The main rationale for rinse-water sampling for bioburden is that it provides an overall picture of equipment cleanliness. Also, bioburden testing of rinse water is typically already a qualified method for testing water systems for bioburden. The biggest weakness of rinse-water sampling and membrane filtration is that the full range of the acceptance criteria is not able to be utilized. For example, if 100 ml of rinse water is used for testing with an acceptance criteria of 100 CFU/mL. The typical number of colonies that can be counted is 300 before Too Numerous To Count (TNTC) is achieved; this only allows an acceptance criterion of 3 CFU/mL before failing to demonstrate that the acceptance criterion is met. In most situations this is not an issue; it may result in the need to test smaller sample volumes (or diluted samples). An alternative is to perform spread-plate or pour-plate microbiological analyses.

Two methods for directly measuring on surfaces are swab and contact plate. For swab samples, the swab can be desorbed and a count made by a pour-plate or spread-plate method. Contact plates are directly incubated and enumerated. The biggest concern with contact plates and swab procedures is potentially exposing product contact surfaces to an unknown media or buffer solution from swabs; thus acceptable removal of this media or buffer solution should be demonstrated before manufacturing can occur. Another concern is that contact plates require flat surfaces.

Most companies use analytical techniques for bioburden involving incubation in an appropriate medium and counting of CFUs. Such a procedure has the disadvantage of only providing a number for CFUs and not individual cells. Sampling and processing of the test sample may affect the reported number of CFUs due to disruption of aggregated cells. In addition, while it is common to report bioburden counts below 20 CFU as quantifiable numbers, it is recognized that enumeration below 20 CFU is not scientifically established. Another alternative is to use rapid instrumental microbiological procedures. PDA Technical Report 33, *Evaluation, Validation and Implementation of New Microbiological Testing Methods* should be consulted for a discussion of rapid methods ***(28)***.

7.7 Analytical Method Validation

This section focuses on analytical method validation for "chemical" residues. Typically endotoxin methods are compendial methods and do not require formal validation but require a confirmation for their application of use or suitability. Microbial methods that are approved microbiology laboratory methods do not require additional method validation.

7.7.1 General Principles

Since one key part of cleaning validation is setting residue limits and then measuring (using an analytical method) the actual residues left on surfaces after cleaning, it is critical that the analytical method be appropriately validated. Method validation is typically accomplished using the criteria in ICH Q2 (R1) ***(29)***. However, the types of assays listed in ICH Q2 do not explicitly cover cleaning validation methods. One approach is to essentially validate analytical methods, much like an "Assay" in ICH Q2, establishing accuracy, precision, specificity, linearity and range, with added determination of limit of quantitation/ limit of detection (LOD/LOQ). LOD/LOQ must be below the acceptance limit for the sample, and ideally is significantly below the acceptance limit so that the robustness of the cleaning process can be established. In addition to the ICH Q2 parameters, sample stability as a function of storage conditions (time, temperature, vial for storage, etc.) may be evaluated if there is a significant interval between sampling and analysis. Specific methods should address possible interferences from other species, such as cleaning agents, which might occur only in the cleaning process.

In cases where a nonspecific method is utilized, it is not necessary to compensate for the lack of speci-

ficity by "other supporting analytical procedures" (as suggested in ICH Q2). The reason for this is that for cleaning validation purposes, the limit value is not a target (as it is for a potency assay); rather the limit is a value *not to be exceeded*. As long as these other species that contribute to the nonspecific response do so in a positive manner (thus increasing the response value), and as long as the total measured value is attributed to the target residue, such complementary methods suggested by ICH Q2 are not required. Furthermore, it is not required to correlate nonspecific methods with a specific analytical method except to the extent that accuracy in the method validation of the nonspecific method may be established using a known standard where the concentration or activity is established by a specific analytical method. While Detection Limit and Quantitation Limit are not part of the "Assay" requirement in ICH Q2, it is critical that these values be at or below the pre-established limit for the residue (otherwise it would not be possible to claim that residues were below predetermined limit values). However, it is not necessary to drive detection or quantitation limits as low as possible; having detection or quantitation limits of 10% or less of the residue limit in the analytical sample is ideal (but not always possible) to establish the robustness of the cleaning process. Assay capability should take into account both the target/limit and the process capability, and provide relevant measurements for both.

When performing carryover calculations it should be ensured that the analytical methods that will be used for cleaning validation are sensitive enough to meet the acceptance criteria. To provide reliable results for carryover calculations, the results should be equal to or above the LOQ. Results between the LOQ and the LOD typically show a higher-than-acceptable variation of the results obtained and are typically reported as less than LOQ.

For companies that use a pass/fail analytical method for meeting cleaning validation limits, analytical method validation is less extensive. In such a procedure, the only conclusion of the analytical procedure is whether the experimental sample is less than or equal to or above the pass/fail value. Accuracy and precision are typically performed only at the residue limit but linearity and range are not performed. Note that in this case, the pass/fail value selected should take into consideration any applicable correction factor due to the sampling method recovering less than 100% from the surface. Such pass/fail methods do not allow collection of relevant data to support a process capability determination to establish action or alert levels for routine monitoring. Pass/fail analytical procedures are more likely to be used in manufacture of early clinical trial materials where a cleaning verification mode is employed. However, such methods can also be used for qualification runs and for routine monitoring.

Analytical method validation protocols may only include validation of the residue in solutions. It may also include sampling recovery studies, although those sampling recovery studies may be performed as separate studies apart from the analytical method validation.

Acceptability of variability of results for parameters, such as accuracy and precision for chemical methods at typical residue levels, are generally much broader than in a typical potency assay. Relative standard deviation (RSD) requirements of 15-20% are typical.

7.7.2 Compendial Methods

Compendial methods do not require separate analytical method validation provided those methods are used within the parameters in the compendia. For example, a compendial method for endotoxin is generally appropriate for measuring endotoxin in final rinse water samples. However, suitability of use of compendial methods should be addressed.

When using swab or rinse samples with a compendial analytical method, items that should be con-

sidered for suitability of use include the validated range, possible interferences from the cleaning process, possible interference from the swab, and recovery of residue from the swab (see **Section 6.1.3).**

When using TOC in rinse-water samples (a compendial method), additional work should be done to support its applicability for test samples where the TOC values could be above 500 ppb or where a linear range is to be established. Just performing system suitability as specified in the USP requirement may not be adequate to demonstrate that the TOC analytical procedure could accurately analyze samples at 1 ppm or 5 ppm. For that reason, analytical method validation as for any other method should be considered. An additional reason for formal method validation for TOC in rinse-water samples is that the USP method is essentially set up as a pass/fail test, not as a quantitative assay.

7.7.3 Visual Inspection

Method validation in this case is actually the determination of a quantitative "visual limit" where visual examination is the *sole* sampling/analytical method and "visually clean" is used as the *sole acceptance criterion* for the given residue in the *absence* of swab or rinse sampling for that residue. If visual examination is used to supplement swab or rinse sampling, such determination of a visual limit is not required. A visual limit *under specified viewing conditions* can be determined by spiking coupons of the equipment surface materials with solutions of the residue at different levels (in $\mu g/cm^2$) and having a panel of trained observers determine the lowest level at which residues are clearly visible across the spiked surface. The significance of such a visual limit is that if equipment surfaces are determined to be visually clean under the same (or more stringent) viewing conditions in a cleaning validation protocol, the level of the residue is below the visual limit. Appropriate viewing conditions include distance, lighting and angle. The visual limit depends on the nature of the residue as well as the nature of the surface (e.g., stainless steel vs. PTFE).

7.7.4 Bioburden Methods

Approved and qualified microbiological lab procedures do not require additional method validation for use in cleaning validation programs. However, suitability for use of such methods in the presence of cleaning process chemicals should be addressed ***(30)***.

7.7.5 Transfer to another Laboratory and Use of Contract Laboratories

Other laboratories (other than the laboratory that originally validated a method) can be utilized to perform an analytical method for cleaning validation purposes. In such cases, a method transfer protocol should be established and executed to determine that the other laboratory can suitably analyze samples using that method. If a method is developed by a contract laboratory and qualification run samples are analyzed by that contract laboratory, then no transfer protocol is required. It is preferable that analytical method validation protocol be reviewed and approved by the pharmaceutical company prior to execution of that protocol. Care should be used in the transfer protocol to first determine whether the measurements between the two laboratories are practically significant before any determination of statistical significance is performed ***(31)***. If an analytical method has been developed and validated *previously* by the contract laboratory, then the pharmaceutical company should review that protocol and the final report to determine the acceptability of the method for its (new) intended use as well as perform an audit of the contract laboratory.

8.0 Maintenance of Validated State

A key part of the validation lifecycle for any system is maintenance of the validated state. A variety of terms are used within the industry for those activities that follow the cleaning process design/development and successful execution of the formal validation protocols. The term used in this Technical Report for those activities is "validation maintenance"; other related terms used in the industry include "continued process verification", "ongoing process maintenance", "ongoing process control", "monitoring", and "continued process control". Validation maintenance is critical for cleaning validation because a lapse, shift, and/or change in the validated state has the potential to adversely impact the quality, safety and purity of subsequent batches of the same or different products. The main tools for ensuring the continued maintenance of the validated state are change control, periodic monitoring and data trending review. Additionally, training is an important area of control for cleaning processes, and it is one of the primary mechanisms for controlling manual cleaning consistency.

In each of these areas, knowledge of the operational parameters and/or design space (see **Section 3.0**) should be applied. Furthermore, application of risk management principles should be used for selection of validation maintenance practices for a given facility or process. Risks to be addressed include not only product quality risks. Note that for formal risk management assessments, the risk focus should be on risks to patients and product quality. However, risks related to business operations and operator safety may be the rationale for certain validation maintenance practices. For example, monitoring of conductivity in the recirculating cleaning solution line may be based primarily on quality concerns. However, provided that such monitoring of the recirculating cleaning solution is done, monitoring of detergent level in a drum may be based primarily on a business risk to prevent interruptions in manufacture. Activities (and the frequency of those activities) to be conducted during validation maintenance should be initially selected during the design/development and qualification stages. However, they may be modified based on new information and/or data collected during routine commercial manufacture. Examples of such information include newly discovered sources of variation or consistent trending data. Maintenance of the validated state should include the cleaning process and equipment, including preventive maintenance and calibration for the equipment being cleaned and the equipment used for cleaning.

8.1 Critical Parameter Measurement

It is of utmost importance to understand the control range of critical parameters used to define the cleaning process. Typically, these include cleaning agent concentration, temperature, flow rate and times for all processing steps. During the design phase, an appropriate level of understanding of the process and its variability should be obtained to design a cleaning process capable of addressing this inherent variability. Once the process is well defined, there are a variety of control strategies that may be used.

One control strategy is to set minimum and/or maximum values for each of the critical cleaning parameters during a cleaning cycle. In this approach, each of the steps of the cycle has a defined proven range or threshold (*lower* threshold or *upper* threshold) that should be measured and maintained during each execution of the cleaning cycle, and each parameter should be within that range or within that threshold. This approach has an advantage in that it is straightforward to implement and control and demonstrates proper performance of the cleaning process on each cleaning run.

Measurement of parameters for purpose of feedback for process control (such as process completion) is discussed separately in **Section 11.3** on Process Analytical Technology.

8.2 Process Alarms

Another practice for validation maintenance is alarming of critical parameters or events. Alarms for

process parameters and/or events are typically based on a quality risk approach but there may be alarms based on business or safety concerns. In an automated cleaning cycle, alarms may be based on a variety of parameters, such as temperature of the wash and rinse solutions, online analytical results of the recirculating wash solution, pressure at the spray device, flow through various circuits, and online analytical results of the final rinse. These are typically automated alarms, in which a light flashes, a buzzer sounds, or the cleaning process is aborted, with the generation of a failure record. When using measurement probes for alarm purposes, the device should have appropriate accuracy and should be maintained in current calibration. There may also be other "nonautomated" alarms, in which observations by an operator trigger a response (e.g., visual observation by an operator that a cleaning detergent drum is empty).

There are a variety of approaches to cleaning the equipment on which an alarm occurred. The cause of the alarm should be investigated. This may be done as part of a Corrective and Preventative Action (CAPA) program. One strategy is that on specified alarm conditions, the cleaning cycle may be restarted. For example, if inadequate cleaning agent concentration occurred (as indicated by an alarm on the wash cycle conductivity), the cleaning cycle can be restarted from the beginning after appropriate actions are taken to ensure that the alarm does not reoccur and that the cleaning effectiveness will not be adversely affected. This is a conservative approach and ensures a complete cleaning cycle is performed, but care should be taken that alarms are noted and trended to ensure cycle performance is not trending towards being ineffective and to better correct repetitive problems. Alternately, the step in which the alarm occurs may be restarted. This approach strikes a balance between ensuring cycle performance and minimizing cleaning time as the entire cycle does not have to be repeated. Automated alarming is generally not done in manual cleaning operations. However, if cleaning agent dilution is confirmed by conductivity, or cleaning agent temperature is confirmed by temperature measurement, measurements outside the specified range can serve as an "alarm." In all cases, it should be ensured that cycles performed *during validation* are not "best case" due to alarm conditions. For example, if equipment is soiled and during the validation runs of the cleaning cycle, alarms occur that result in multiple additional rinse steps being completed, this cycle may no longer be representative or worst case but may be a best case.

8.3 Change Control

A change control system is critical for ensuring maintenance of the validated state for cleaning processes. The change control system should cover all key parameters and components of the cleaning system to ensure that all changes with a potential to impact maintenance of the validated state are evaluated. This includes not only changes in the cleaning process but also changes in equipment and changes in the manufacturing process (e.g., a change in temperature in a manufacturing process) that might affect the performance of the validated cleaning process. Quality preapproval and tracking of changes are key requirements for this system.

The change control system should provide for a review of each change by an interdisciplinary team. This should include a review of current validation for the equipment being changed, and depending on the nature of the change, may result in laboratory, pilot scale and/or commercial scale evaluations. This may also involve a review of the relevant sections of any risk assessment previously done. Significantly major changes may result in the decision that the new cleaning process requires separate validation as a new process. There are some important considerations for designing the test plan to verify changes; review of the process design considerations will assist in this evaluation. First, control parameters should stay within their validated ranges. If changes are made to extend or widen a validated range, an evaluation should be made to determine the nature and extent of testing (if any) necessary to change that range. For example, if the pump on a CIP skid is validated to deliver wa-

ter between 60 and 70 liters per minute, and the desired change is to increase the flow rate to 70-80 liters per minute, new validation testing is required to verify that the pump is capable of delivering the desired flow before validation of the cleaning cycle can occur. Second, the acceptance criteria for analytical methods should remain unchanged from the previous validation unless there is a justified reason for the difference. This is to ensure that changes result in maintenance of the validated state rather than creation of a new state, which may require significant testing to ensure it is still validated. Finally, reduced sample sites and/or fewer analytical methods may be appropriate in many cases to confirm validation maintenance based on a change. For example, if the effect of the change is only on bioburden then it may be appropriate to evaluate only bioburden in studies that evaluate the effects of the change. These differences should be justified in the testing plan/protocol.

8.4 Routine Monitoring

Another tool for ensuring maintenance of the validated state is a risk-based routine monitoring program. A routine monitoring program may provide analytical data to be trended (see **Section 8.5** below), such as by SPC. In most cases involving automated processes, the data are provided by the automated equipment itself. For example, data may be generated by the CIP skid on wash-solution conductivity, final rinse conductivity, temperatures, times, flow rates and pressure. In other cases, separate sampling may be established for data collection, such as rinse analysis by UV/Vis, HPLC, or TOC. Visual examination after each cleaning process is another type of routine monitoring. Visual inspection after each cleaning process typically does not involve disassembly of equipment solely for the purpose of that inspection.

A documented risk-based approach should be used to optimize compliance in an efficient manner. This could include leveraging family or grouping approaches, reduced sample sites and reduced analytical methods. Leveraging in this manner is most common on cleaning processes which were grouped for qualification purposes but it may also be done for cleaning processes which were qualified separately. In both cases, all members of the group should be considered for routine monitoring activities in a risk-based approach. When defining these approaches, the inherent risk associated with a given cleaning process and historical experience/data should be considered. For example, when performing the initial validation on process equipment, residues of an active ingredient may be measured via a variety of swab and rinse samples. However, with the proper data analysis, it may be appropriate to measure using only rinse sampling during routine monitoring. However, it may be appropriate for cleaning of highly hazardous drug active ingredients (as compared to cleaning of drug active ingredients that are not highly hazardous) to include more sampling for residues as part of routine monitoring after completion of the qualification runs.

8.5 Data Trending and Review

Trending of cleaning cycle performance, analytical data from routine monitoring, and alarms are another recommendation to ensure continued cleaning cycle performance. Data that is trended can be continuous data (such as final rinse water analysis) or discrete data ("yes/no" data such as occurrence of an alarm). When trending any of these data sets, procedures should be in place to initiate an investigation when adverse trends are observed even if ineffective cleaning cycles have not occurred. Trending of cleaning cycle performance data is important for identifying potential cleaning cycle issues *before* they result in ineffective cleaning cycles. For example, a slowly increasing trend in the final rinse analytical result may not be indicative of an *ineffective* cleaning process. However, such a trend should require an investigation of the cause. In the example given, it may be that the spray device is becoming clogged, in which case it should be cleaned, and appropriate steps should be taken to prevent clogging in the future. On the other hand, it may be a result of a fouled sensor, such as a conductivity

sensor. Alarm monitoring and trending will help indicate cycle failure although alarm data will not proactively identify potential issues. The incidence of all alarms should still be trended to determine if additional process controls are required to reduce the frequency of alarming. Data trending may also serve as an important input for a continuous improvement program.

For data trending, there should be appropriate criteria established for action and/or alert levels. It is advisable to obtain guidance from a statistician to determine the appropriate number of data points necessary to obtain a statistically relevant data set. These values are typically less than any pass/fail acceptance criteria established for the qualification runs. Statistical process capability studies, based on multiple (e.g., 20-25) data points, may be used to establish action/alert levels. Since such extensive data may not be available for initial commercial manufacture, data from development runs and/or sufficiently similar cleaning processes may be used to establish tentative action/alert levels. Appropriate technical judgment should be utilized in establishing action/alert levels that are *practically* significant and not just *statistically* significant. For example, consistently obtaining "zeroes" for rinse bioburden data for the cleaning process may not alone be sufficient to require a "one-time" value of 3 CFU to be a significant event which needs an investigation.

8.6 Evaluation of Cumulative Changes

Review of the *cumulative* impact of changes on a system should be considered. Such a review may be initiated based on data/events from the cleaning process or may be time-based. One approach is to include a review of cumulative changes for every change control event. This review should provide evidence that the cleaning cycle continues to meet specified requirements despite multiple small changes, each of which was appropriately approved. It is possible that many minor changes (each deemed to have no impact on the validated state) could have an impact when considered in total. This review of cumulative changes may involve two approaches. First, a documented analysis (i.e. review of the changes and the impact these changes will have on other parts of the process) of the changes should be undertaken. Second, process performance and alarms should be monitored to ensure continued maintenance of the validated state and system performance.

8.7 Training

Training after the initial qualification runs should be done to help assure maintenance of the validated state. One type of training may involve training on a procedure revised for either clarification or for a cleaning process change. Another type of training is retraining of a previously trained operator because of suspected operator error. A third type of training is retraining on a regular basis for manual cleaning processes. This latter training may be done on a regular basis to avoid process "creep". Of course, training of any *new* (previously untrained) operators should also be done. Training should cover cleaning process operators, sampling personnel, and analytical personnel as applicable.

8.8 Periodic Review

As part of lifecycle validation, it is common practice to perform an overall periodic review of the validation state. The frequency of such a review will depend on a risk assessment. Such a review typically involves a review of data collected as described in **Sections 8.1** through **8.7** above. In addition, it typically involves a review of any changed regulations as well as any change in common industry or inspectional practices that might be considered part of *current* Good Manufacturing Practice. This periodic review should be documented and should include a conclusion as to the validation status of the cleaning process. It may also include recommended or planned improvements in the cleaning process.

Historically, it was considered acceptable to perform periodic revalidation on cleaning processes in

lieu of routine monitoring and periodic review. However, the approach of revalidation yields a much less robust picture of the state of control of the cleaning process and may be more resource-intensive. Revalidation as a concept is no longer used by some regulatory agencies because of a preference for a lifecycle validation approach. Under a lifecycle validation approach, a significant change in a cleaning process involves not the revalidation of the previous process, but rather validation of a new process. Such validation of a new process, however, may rely on data from the old process based on it being sufficiently similar.

9.0 Documentation

Documentation is pivotal to cleaning process knowledge management. Documentation of cleaning validation activities will vary with individual company practices. This is particularly the case in terms of where data, reports and other documents are stored and how they are retrieved. There might be variations among companies in terms of determining at what stage of validation (i.e., design/development, qualification, and validation maintenance) those documents are considered. All data and documents relevant to a determination of the extent of control and consistency of a cleaning process should be appropriately controlled and consistent with GMP regulatory requirements and with the company's quality system. This system should be such that those documents can be readily retrieved. This documentation should be part of, or consistent with, a company's quality management system. A procedure on documentation, with specifics for cleaning validation documents, should be considered for knowledge management.

This section will cover documentation for a high-level cleaning validation master plan and/or policy, for design/development, for qualification, and for validation maintenance. **Figure 9.5-1** contains the typical steps in a cleaning validation process flow where appropriate documentation should be considered.

9.1 Cleaning Validation Master Plans

It is good practice to have a document or documents near the top of the cleaning validation documentation hierarchy that broadly define the expectations for a cleaning validation program. This document is often called the "cleaning validation master plan". Such a master plan is not a regulatory requirement but is a practical "requirement" in order to facilitate regulatory inspections as well as to ensure consistency of execution within a facility.

The plan should provide a description of responsibilities and activities for the planning and execution of cleaning validation. This is best accomplished by a specific cleaning validation master plan. The cleaning validation master plan could be described in detail or referenced as a separate document in the overall site validation master plan. The cleaning master plan may be all-encompassing. An alternative approach is to have a high-level cleaning validation policy and then have a cleaning validation master plan that has more detailed explanations of the validation requirements. This approach is common for multinational companies where a cleaning validation policy is set at the corporate level. Individual sites will prepare master plans consistent with that policy, but with requirements more appropriate for the manufacturing situation at that site. If this approach is used, care should be utilized in the higher level policy so as not to set policy requirements that may not be appropriate for every site.

These documents are living documents that should be reviewed and updated as needed and on a defined frequency specified in the master plan. A report to the plan may be written periodically to summarize the major activities executed under the plan during that interval.

The cleaning master plan will describe the overall plan, rationale and methodology to be used in performing cleaning validation. The plan should provide a high-level description of the cleaning validation philosophy and strategy that will support the validation activities performed at the site. Detailed procedures on the execution of cleaning validation will be in individual protocols. The plan will define the efforts required to ensure the cleaning program complies with current Good Manufacturing Practices (CGMPs). The validation activities are documented according to the requirements of the plan to provide sufficient scientific rationale to assess the suitability of the cleaning program in order to consistently clean equipment to the required specifications. During a regulatory inspection, an inspector may ask to review the master plan and then look at the specific validation protocols and final reports to determine if the plan is appropriate and to assure that the elements of both the plan and individual protocols are being followed.

9.1.1 Elements of a Comprehensive Plan

The master plan should address each important aspect of the cleaning validation program. Elements of a master plan and the appropriate details provided for those elements will depend on the practices of the specific facility. One approach is to include more detail in the master plan while another approach is to include that level of detail for procedures consistent with the master plan. Elements of a master plan may include, but are not limited to, the following topics:

- Purpose of the plan
- Scope of the cleaning validation program
- Designation of responsibilities
- List of equipment to be validated
- Definitions and glossary of terms
- Means of cleaning documentation (e.g., procedures and records)
- Prerequisites to cleaning validation (e.g., equipment and utility qualifications)
- Spray device coverage testing
- Use of various cleaning systems (e.g., CIP, COP, mechanical washers or manual cleaning)
- Cleaning reagents and mechanisms
- Cleaning cycle development requirements
- Cleaning equipment lists
- Product list
- Cleaning SOPs
- Precleaning methods
- Conditions for use of artificial or surrogate soils
- Definition and use of "worst-case conditions" associated with a cleaning process (e.g., flow rates or step durations)
- Description of family approach and grouping of products/equipment/systems based on similarities, including an approach to determine "worst-case product" based upon attributes that impact cleaning (e.g., solubility of all components in the "soil")
- Use of dedicated or shared equipment; single use (disposable) equipment
- Definition of circumstances in which cleaning verification is preferred or acceptable (e.g., clinical stages)
- Strategies and definitions for indirect product contact surfaces
- Cleaning of components and single-use equipment
- Use of quality risk management to determine the scope and extent of validation activities
- Establishment of design space based on cleaning parameters and use in ongoing monitoring
- Use of mock, blank, or placebo runs
- Equipment hold study approaches (e.g., dirty hold, clean hold or storage hold)
- Microbial contamination (e.g., bioburden and endotoxin)
- Sampling techniques (e.g., visual inspection, rinse sampling or swab sampling)
- Training/qualification for sampling techniques
- Analytical methods (e.g., validation and recovery requirements)
- Rationale for the use of product-specific assays and nonspecific assays
- Rationales and formulas for limits for process residues, microbial contaminants and cleaning agents
- Validation maintenance (including routine monitoring, change control, and periodic review)

- Attachments/appendices (e.g., various tables or lists of items within the realm of the plan such as a responsibility matrix)
- Requirement for reassessment of cleaning validation master plan
- Roadmap or summary of current status and upcoming plans
- References

Note that this is a comprehensive list. Some items listed may not be applicable to a given manufacturer. Some items may be maintained by a manufacturer in a system outside the cleaning validation master plan.

9.1.2 Harmonization of Site Cleaning Validation Programs

For a product made at more than one site, where appropriate, the cleaning requirements should preferably be the same. However, if the process equipment scale , the type of cleaning equipment available, analytical equipment, and/or cleaning process is different (e.g., CIP skid vs. manual), the programs can only be harmonized to a limited degree. The acceptance criteria may differ for any limit that is based on batch size and equipment surface area. The same would also apply to some degree if a contract manufacturer were making the same product. However, there is an additional consideration in that the contractor is also obliged to follow its own master plan. A contract manufacturer may validate their cleaning process using techniques and procedures that differ from those of the sponsor but the resulting validation must be compliant and must meet appropriate regulatory expectations. Any critical differences should be addressed upfront in a quality agreement with the sponsor. The ultimate responsibility for the cleaning validation does reside with the sponsor.

9.2 Documentation for Design/Development

In a risk-based environment, it may be appropriate to begin the design/development stage of cleaning validation with a risk assessment to provide a rationale for the development plan as well as to identify CQAs and CPPs. This assessment will be different for an entirely new cleaning process as compared to a consideration of an existing cleaning process for a new product.

The output of laboratory studies (if any) will typically include initial selection of the cleaning agent, cleaning agent concentration (if applicable), temperature and time of the washing step (see **Section 3.0).** It may also include stress studies to identify the robustness of those selected parameters. Laboratory studies may also be used to determine the nature and/or characteristics of residues (such as degradation of the API) following the cleaning process. Reports for laboratory studies should have clear conclusions with references to documentation for supporting data. The output of lab studies may also be leveraged to aid in equipment design.

The output of pilot-scale studies (if any) will typically include a confirmation and/or modification of the basic cleaning parameters, plus an evaluation of any engineering issues (such as dead legs) that may affect the selection of those cleaning parameters. Reports for pilot-scale studies should have clear conclusions with references to documentation for supporting data.

Any studies on full-scale equipment are generally performed to collect data not practical in a pilot-scale or lab-scale study, to investigate any possible issues where lab-scale data may not reflect accurately performance on full-scale equipment, and/or to confirm the performance of the cleaning process on full-scale equipment prior to qualification runs. Reports for full-scale studies should have clear conclusions based on documented supporting data references. For studies on full-scale equipment, cleaning verification should be performed in order to release the equipment for subsequent manufacture of a commercial product.

Clinical batches may be made on pilot-scale and/or full-scale equipment. The cleaning verification data from such studies should also be leveraged to support conclusions of the design/development report.

The output of design/development stage should be both a development report (also called a technology transfer report) and a draft cleaning process procedure (SOP). It may also include a risk assessment report based on the cleaning procedure, although this risk assessment may be done as an initial step in the Qualification stage.

9.3 Documentation for Qualification

Documentation for the Qualification stage starts with Commissioning and IQ/OQ protocols/reports on the equipment utilized for cleaning (assuming that Commissioning, IQ and OQ for the equipment to be cleaned are already done as part of the process validation). The emphasis for this stage is design and execution of the protocols for the validations runs (sometimes called process performance qualification, or PPQ, runs). Validation runs should not be considered experiments to gain new information but are a confirmation of what is known. Documentation that may be needed prior to preparation of the protocol may include:

- Validation strategy, including rationale for product and/or equipment grouping
- Draft cleaning SOP, including CPPs
- Acceptance criteria and how those criteria were established
- Analytical methods and their validation
- Sampling methods and sampling sites (locations)
- Sampling recovery studies
- Selection of protocol challenges, including hold times
- Rationale for the selection of number of validation (PPQ) runs
- How equipment cleaning is to documented
- Responsibilities for execution of the protocol
- Training of operators, samplers and analysts on applicable procedures
- Plans for validation maintenance (see **Section 8.0**)
- Plans for equipment and product disposition during the protocol execution.

Note that the number of validation (PPQ) runs should be based on cumulative knowledge based on data collected during the development and qualification stages, and ordinarily is not based on a statistical evaluation.

The next document developed is the protocol itself. One approach is to include all the documentation covered in the prior paragraph in the protocol itself while another approach is to only put in the details critical to execution of the protocol and have references in the protocol to the supporting rationales/data that are in separate documents.

Interim reports may be written for each validation (PPQ) run. The last document developed for this stage is the final report, summarizing the results of protocol execution with a conclusion as to the state of control of the cleaning process. The final report should also include documentation of conclusions of any investigations of deviations. It may also include recommendations for improvements, including changes in the validation maintenance program.

9.4 Documentation for Validation Maintenance

Documentation for the validation maintenance stage will depend on activities selected for this stage.

It should include reports related to the following activities, as applicable:

- Alarms and alerts, including investigations and corrective/preventive actions
- Routine monitoring, including trending of data and evaluation of such trending (may include statistical evaluation)
- Change control
- Deviations, including investigation and corrective/preventive actions
- Evaluations of cumulative changes (which might be as a result of a deviation investigation or a periodic review)
- Training and retraining
- Periodic cleaning process review
- Risk assessments relating to any process changes or shifts.

Cleaning log records (such as cleaning log books or cleaning batch records) are generally a GMP requirement and should also be considered.

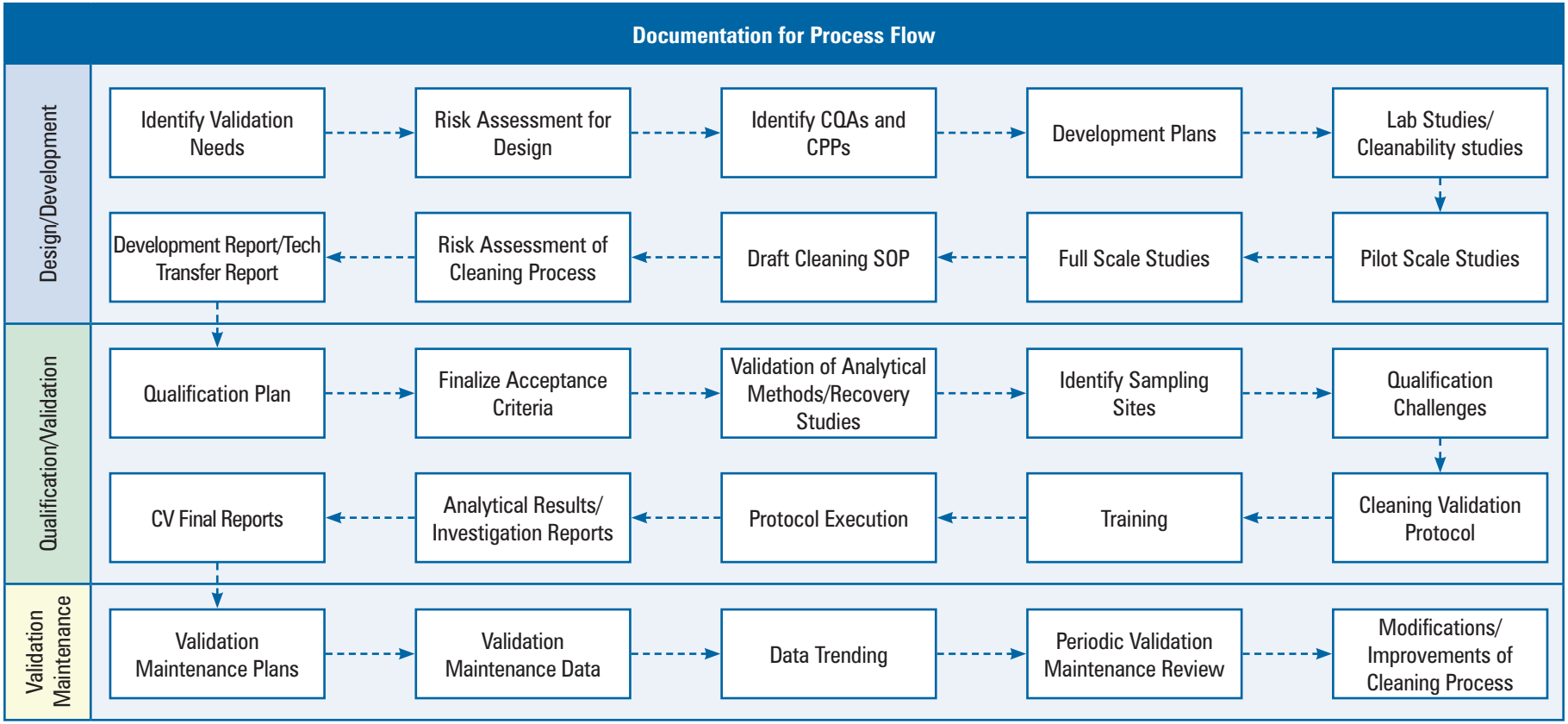
9.5 Other Documentation Considerations

Whenever a risk assessment is performed, it is critical that risk communication be made to departments and/or functions affected by the risk assessment. Documentation of events, deviations, failures, and/or investigations involving a cleaning process should follow approved practices within a company for such documentation.

Cleaning validation final reports may not be part of a regulatory filing. The requirement for completion of cleaning validation will vary by regulatory authority and nature of the product. In the USA, CDER likes to at least see a plan for cleaning validation as part of the PAI, but CBER requires cleaning validation summaries as part of the BLA filing.

Documentation for cleaning verification follows the same principles as for cleaning validation except that the extent of design/development may be as appropriate for a one-time cleaning activity.

Figure 9.5-1 Documentation for Process Flow



10.0 Special Considerations

10.1 Cleaning Agents

A variety of cleaning agent options is available. These include water, organic solvents, commodity alkalis and acids, and formulated detergents.

10.1.1 Types

10.1.1.1 Water

Although the typical use of water is in the prerinsing, post rinsing, and preparation of use-dilutions, water is also used as a sole cleaning agent for readily water-soluble residues. As a general rule, the quality of water used in the final rinse should be at least as good as the water used in the manufacturing of the drug product. The water quality used in cleaning should also meet the chemical, microbiological and endotoxin levels as appropriate for the application.

10.1.1.2 Organic Solvents

Organic solvents, such as methanol, are used for cleaning in small-molecule API synthesis processes. Solvents are chosen based on the solubility of the manufacturing soils in the solvent. The cleaning process typically involves agitating the solvent in the reactor vessel, circulating it through pipes, and refluxing the heated solvent through overhead risers and condensers. The issue of flammability should be considered for organic solvents. Organic solvents, like isopropyl alcohol, are also used in finished pharmaceutical manufacturing for manual cleaning of parts and to facilitate drying of surfaces.

10.1.1.3 Commodity Alkali

A commodity alkali, such as sodium hydroxide, is often used for the alkaline wash step. The high pH and alkalinity of sodium hydroxide solutions may enhance solubility of organic process residues and, in some cases, facilitate hydrolysis. Sodium hydroxide is also widely available, relatively inexpensive and, being a single component containing no organic carbon, is relatively easy to analyze and validate for cleaning-agent removal. The higher pH of sodium hydroxide also facilitates the precipitation of salts or oxides of such ions as calcium, magnesium and iron if those ions are present during the cleaning process. However, commodity cleaners, such as sodium hydroxide, may have limited effectiveness for tenaciously adhered or baked-on residues. They also have limited wetting characteristics and soil-suspending ability.

10.1.1.4 Commodity Acids

An acid washing step may be used alone for cleaning. The addition of an acid wash step after the caustic wash/rinse may overcome precipitation and buildup of inorganic compounds, improve rinsing, and help broaden the spectrum of soils cleaned (although at the expense of adding another cycle). In addition, maintaining a clean surface and limiting the deposition and buildup of iron oxides or other contaminants may help minimize the potential for stainless steel corrosion and rouge formation.

10.1.1.5 Formulated Detergents

Formulated detergents are multicomponent cleaning agents that take advantage of several different cleaning mechanisms, thus providing broader spectrum effectiveness. In addition to the mechanisms of alkalinity and hydrolysis offered by a commodity caustic, a formulated alkaline detergent might provide improved wetting and soil penetration, emulsification, chelation of calcium, iron oxide or other inorganic ions, and might facilitate dispersion of particulates in the wash step.

10.1.2 Factors in Selection

A number of factors need to be considered when selecting cleaning agents for CGMP applications. These include:

10.1.2.1 Broad Spectrum Effectiveness

The cleaning agent should be effective at removing the residues that may range from single components to complex mixtures of various chemistries that constitute a product's active ingredients, excipients, degradants, and other contaminants. A broad-spectrum cleaner may also facilitate more effective grouping strategies.

10.1.2.2 Substrate Compatibility

The cleaning agent should be compatible with the various equipment substrate materials, such as stainless steel, polymers, glass, and soft metals.

10.1.2.3 Stability and Shelf Life

To ensure consistent performance after transportation and storage, cleaning agent stability and shelf life under those exposure conditions should be considered.

10.1.2.4 Analyzability

Cleaning agents should be analyzable and quantifiable down to the acceptance criteria established.

10.1.2.5 Disposal

Cleaning agents should meet the local waste water discharge requirements such as limits on pH, phosphates and heavy metals. When organic solvents are used, air emission requirements may need to be considered.

10.1.2.6 Safety

Particularly for cleaners used for manual cleaning applications, appropriate personal protective equipment may be required.

10.1.2.7 Toxicity

Cleaning agent toxicity is not only important for personnel safety during cleaning, but also is used in determining the residue limit and consequently cleaning process efficiency.

10.1.2.8 Rinsability

Cleaning agents should be free-rinsing. Cleaning agents that foam can be difficult to rinse and may also cause pump cavitation in CIP systems and COP washers.

10.1.2.9 Quality

Cleaning agents should have a specification, be lot-traceable, and preferably be manufactured using CGMP practices with appropriate change control policies.

10.2 Nonproduct Contact Surfaces

Nonproduct contact surfaces may be defined in different ways by manufacturers. For surfaces with no product contact (e.g., floors, walls, outsides of process equipment), there should be cleaning procedures. However, these cleaning processes are generally less critical and do not require cleaning valida-

tion. Cleaning for these nonproduct contact surfaces may be repeated in full or in part if the cleaning process results in visible and/or gross levels of residual soils.

There are other nonproduct contact surfaces which may contact the product *indirectly,* such as by a vector or by an airborne route. These are sometimes called "indirect product contact surfaces". Examples of these types of surfaces might include lyophilizers, equipment used solely to manufacture and transfer buffers, media, and excipients, and stopper bowls. These indirect product contact surfaces should be included in the cleaning validation program. However, because of the limited impact of these indirect product contact surfaces, requirements for cleaning validation, such as limits, may be different from cleaning validation for *direct* product contact surfaces. A risk assessment should be utilized to define the requirements, which will depend on the specifics of the manufacturing situation. For example, for highly hazardous drug active ingredients, cleaning validation of nonproduct contact surfaces may be performed in order to document any potential of airborne transfer to another product as well as for operator safety reasons ***(12).***

See **Section 10.9** for information related to secondary packaging equipment surfaces.

10.3 Process Analytical Technology

Process Analytical Technology (PAT) is defined by the U.S. FDA to be "a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e. during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality" ***(32)***. The U.S. FDA further notes that "the term 'analytical' in PAT is viewed broadly to include chemical, physical, microbiological, mathematical, and risk analysis conducted in an integrated manner." The use of a PAT approach may replace traditional validation approaches.

Much has been published about PAT in general and about PAT in many processes; the reader should investigate current literature for a general background on PAT. However, there are limited publications about PAT in cleaning processes and cleaning validation as compared to PAT for other manufacturing operations. The use of a feedback loop from the analytical measurement to control a cleaning process or cleaning process step is the point of using PAT. It should be noted that consistent with PAT principles, the timely measurement could be in-line, online or at-line.

10.3.1 Timely Measurements

"Timely measurements" have long been used in cleaning processes to assist in the design of *rinse cycle times* in automated CIP systems. For example, a common practice in the design of the rinsing process using cleaning solutions or products with high conductivity values has been to measure conductivity of the final rinse as a function of rinse time. If evaluated over several cleaning process runs in the design phase, a minimum time to consistently complete the rinsing process can be effectively determined. A safety factor (additional time) may be included as part of this determination. While such a study in the design phase would be appropriate for a PAT application, unless it combines the timely measurement with a feedback mechanism to control the cleaning process during commercial cleaning processes, it would not be considered to be a PAT. As described *in this paragraph*, the purpose of the timely measurement is not to control the rinsing process but to assist in selecting a *fixed* rinse time.

10.3.2 PAT for Cleaning Process Control

The more relevant use of PAT for cleaning processes is the use of a timely measurement to define the completion of a cleaning process. In this case, the achievement of a certain analytical measurement is a controlling mechanism for completion of that process. In the situation referred to previously about measuring conductivity online, if it is possible to determine through experimentation and modeling that

the achievement of a certain conductivity correlates in a statistically significant and operationally meaningful manner with the end of the rinsing process, conductivity could be employed in a PAT approach. That is, the rinse time is not fixed but could be variable depending on the time needed to achieve that predetermined conductivity value. In addition, consistent with PAT principles, it would be expected that the achievement of that conductivity value would be within a defined time window. The U.S. FDA PAT guidance ***(32)*** states "Within the PAT framework, a process end point is not a fixed time; rather it is the achievement of the desired material attributes. This, however, does not mean that process time is not considered. A range of acceptable process times (*process window*) is likely to be achieved during the manufacturing phase and should be evaluated, and considerations for addressing significant deviations from acceptable process times should be developed." In both cases, a final conductivity is recorded and a final rinse time is recorded. However, in the traditional approach, time is the step-controlling parameter and conductivity is the monitoring parameter. In a PAT approach, conductivity could be the step-controlling parameter and time would be the monitoring parameter. Lack of achieving the desired conductivity within the time window should result in an investigation under a CAPA program.

Another example of a PAT application for cleaning is in the use of organic solvent cleaning in small-molecule API synthesis. In this situation, the active ingredient in the solvent may be measured using online UV spectroscopy. The achievement of a low absorbance value, corresponding to the limit of the active in the rinse or solvent reflux sample, may be used to determine the process completion.

Sometimes there is an objection to the use of PAT in this way because it seems to violate the cleaning validation principle of not cleaning until clean (or testing until the equipment is clean). However, one of the features of PAT is that traditional rules of what is done for validation may not apply. As noted in the U.S. FDA's 2011 Process Validation guidance, "In the case of a strategy using PAT, the approach to process qualification will differ from that used in other process designs" (***10***).

10.3.3 Additional Considerations for Online Measurements

It should be clarified that online methods by themselves do not necessarily constitute PAT. As discussed previously, online measurements (such as UV spectroscopy or conductivity) of a final rinse can be a routine monitoring tool in a cleaning process step *without* controlling a process step. Such online measurements, even though they don't control process completion, may be used as a means of cleaning verification after each cleaning event.

10.4 Clean Hold Considerations

Following cleaning, equipment that is to be reused should be stored in a manner to protect it from contamination during storage. Clean hold time is the time from the end of cleaning until subsequent use of the equipment, which may be product manufacture or may be a steam-in-place (SIP) cycle. "Clean hold time" is different from "dirty hold time" in that dirty hold time should be evaluated in the basic cleaning validation protocol as a worst-case condition or challenge. Clean hold time may be included as a second part of the basic cleaning validation protocol or may be considered as a separate protocol (apart from the basic cleaning validation protocol). The cleaning process validation study and the clean hold time study are related in that the data for bioburden at the end of the cleaning process also serve as the "time zero" bioburden data for the clean hold study.

The major concern with the clean hold time is the possibility of recontamination from external sources and the possibility of microbial proliferation because the equipment is wet with water during the clean hold period. The major *regulatory* concern is the control of microbial proliferation during the storage of equipment. If the microorganisms that proliferate are Gram-negative bacteria then issues with endotoxin may also arise. External sources of recontamination can be prevented by closing the

dry equipment or by wrapping the dry equipment in plastic (or storing in plastic bags). Selection of an area for storage (including temperature and humidity) is also important for preventing external recontamination. Water in the equipment can come from lack of drying at the end of cleaning, condensation of water onto equipment surfaces from humid air because of a temperature drop, and external sources (such as splashing water onto cleaned equipment because the equipment is stored next to a wash sink).

Criteria used to determine acceptability after storage under defined conditions may include lack of microbial proliferation, endotoxin level and visual examination. A major regulatory concern is the control of microbial proliferation during the storage of equipment. While based on a risk assessment it may be possible to justify not measuring bioburden for a clean hold time before a sterilization process, it may be prudent to measure bioburden after the clean hold time to ensure that the subsequent sterilization is not excessively challenged. This is also important from the standpoint of the control of pyrogens from Gram-negative bacteria, which may not be removed or inactivated by sterilization processes. An additional issue is to insure that plastic wrap or bags are intact and not compromised during the clean hold storage. Storage instructions should be specified in a control document, such as the cleaning procedure or approved storage procedure.

The best procedures are to store cleaned equipment in a dry state or in a solution that inhibits the microbial proliferation. If equipment is to be stored in a dry state, manufacturing controls should be in place to ensure that equipment is sufficiently drained and dried upon completion of the cleaning process, as well as to minimize the amount of condensed water accumulation in the equipment *after* cleaning due to equipment cooling. In addition, it is preferred that equipment be stored in a manner to prevent external recontamination. If stored in a dry state and if protected from external contamination (e.g., by sealing the equipment or by covering any openings with appropriate "GMP" covers), formal studies to demonstrate lack of microbial proliferation may not be necessary. Based on sound scientific principles, microorganisms will not proliferate on clean, dry surfaces. If stored in an inhibiting solution, the solution should be known to inhibit microbial growth (such as dilute caustic) or data should be developed to demonstrate inhibition. Recirculation of the storage solutions may also assist in microbial growth inhibition. Procedures should be in place to adequately remove that inhibiting solution from equipment prior to use.

If the equipment is stored with a possibility of water in all or parts of the equipment, there are two common strategies to control microbial proliferation during the storage of equipment. One strategy is to establish an acceptable time between the end of cleaning and the beginning of the next use (which may be sterilization, sanitization, or a manufacturing process step) by performing a clean hold validation. After a predetermined storage time, sampling by a suitable method is performed and the post-hold data is compared to the data at the beginning of storage. If rinse sampling is used, it should be ambient temperature water so that what is measured is the bioburden remaining on surfaces (the use of a hot water rinse may reduce the bioburden in the rinse solution). Bioburden (and possibly endotoxin) levels in the equipment are measured to ensure that levels would not challenge the sterilization or sanitization procedures or exceed in-process manufacturing specifications. Since purified water or WFI is not an ideal medium for bacterial growth, another approach is to require the use of the cleaned equipment within a short time period, such as one shift or 24 hours, such that microbial proliferation is not likely to occur.

If clean hold validation is not performed, or if the validated clean hold time is exceeded, a validated water (usually hot purified water or WFI) flush may be used before sterilization, sanitization, and/or use of the equipment to reduce microbial proliferation that might have occurred during storage to an acceptable level before further manufacturing or processing on the equipment. After the water flush, sampling (by rinse, swab or plating) is performed. Bioburden (and optionally endotoxin) levels

in the equipment are measured to ensure that levels would not challenge the sterilization or sanitization procedures or exceed in-process manufacturing specifications. Another approach is to perform additional bioburden sampling to document that microbial proliferation has not occurred.

For clean hold time studies using rinse water fed from process lines, a few common approaches for establishing the acceptable amount of rinse water to use are based on the minimum working volume of the system or the minimum CIP rinse based on the design. Bioburden values in rinse sample should be compared to the measured bioburden values based on the equivalent rinse sampling at the beginning of storage. It is preferable to collect the entire volume of rinse solution and agitate it for a specified period of time to ensure homogeneity before collecting the sub-sample for testing. This collection of the entire rinse sample may be done in the process vessel itself or in an external vessel.

Validation of clean hold studies on a given piece of equipment is applicable to all products using that equipment and to all cleaning processes for that equipment, provided the final state of the cleaned equipment and the storage conditions are consistent. If a validated clean hold time is exceeded, an assessment should be made as to the need for corrective action. Appropriate corrective actions before use or further processing may include cleaning the equipment again using a validated cleaning process or using a validated hot water rinse (as described above) to bring bioburden to an acceptable level. If any changes to the equipment, manufacturing processes and/or cleaning procedures are made, the impact of these changes on the clean hold studies should be evaluated.

If cleaned equipment is to be stored for an extended period of time in an area that is not controlled, it is even more important that the equipment be stored in a dry state because of possibilities of significant bacterial or mold proliferation. In any case, there should be a procedure in place to deal with the return of such equipment to active use. This may be an individual determination on a case-by-case basis, it may be treating the equipment as if it exceeded the dirty hold time, or it may be treating the equipment as if it exceeded the clean hold time. A risk assessment for the specific facility will help determine which option is utilized.

10.5 New and Used Equipment

Introducing additional equipment into a firm's established cleaning validation program presents several issues which will require careful consideration. Factors such as equipment design, materials of construction, modes of operation and product-contact surface area are likely to influence decisions on how the incoming equipment will fit and on what steps should be taken to integrate the equipment into the cleaning program. Additionally, whether the equipment is of new construction or was obtained as a used piece of equipment should be considered when developing steps to utilize the equipment. These considerations for new and used equipment may also be applicable to equipment that has been repaired or refurbished.

10.5.1 New Equipment

When adding new equipment to a cleaning program, some points to consider are as follows.

10.5.1.1 Cleaning Procedure Development

If the new equipment is sufficiently similar to existing equipment, design/development for the new equipment may leverage knowledge from that existing equipment. If the new equipment is not similar to existing equipment, additional cleaning development work may be required. The design characteristics and operational parameters of the new equipment may present hard-to-clean areas or operating ranges not previously encountered in existing equipment.

10.5.1.2 Post-Installation Cleaning

Following the installation of the new equipment, cleaning is typically required in order to remove any grease, dust or other debris. Manufactured product residues are not usually a concern at this point. The effectiveness of this cleaning may be shown using a visual inspection, water-break evaluation, a white-glove (or black-glove) test, and/or various chemical tests (such as TOC and conductivity). This cleaning is not typically validated, but is verified (see **Section 4.4** on "Cleaning Verification").

10.5.1.3 Grouping Impact

If a firm employs a grouping approach regarding equipment, the addition of new equipment into the production facility may have an impact on established equipment groups. See **Section 4.3** "Grouping/Family Approach" for more information.

10.5.1.4 Limit Calculation Impact

The addition of new equipment into an established train, line or group may have an impact on acceptance limits based on the increase or decrease of product-contact surface area. Calculations should be reviewed for any impact and any changes implemented through a change control program.

10.5.2 Used Equipment

When adding used equipment to a cleaning validation program, the points noted in the previous section about new equipment apply. An additional point to consider for used equipment is equipment history. It is desirable to have as much information as possible about the compounds that were previously manufactured in the equipment. Some information of interest would be the type of compound (e.g., pharmaceutical or pesticide) and the hazards and/or toxicity of the compounds. That information may be used to determine an acceptable cleaning process for the used equipment, and to set acceptance limits for those compounds for a cleaning verification evaluation following the cleaning process.

If little to no information about the previous compounds is available, it may be possible to identify potential manufactured products by FTIR analysis of swabbed surfaces. Additional surface modification steps (e.g., descaling, pickling, passivation, reglassing, repolishing) may be taken to assure the cleanliness of the equipment. An evaluation of cleanliness may also entail TOC analysis (as a general measurement of equipment cleanliness) and/or FTIR analysis of sampled surfaces (to confirm removal of any potentially objectionable organic residues identified in the precleaning FTIR analysis). The justification for a firm's decision should be captured in a documented risk-consideration. In some cases, the additional cost of the steps taken for used equipment may negate any cost benefit; therefore, this consideration should be made well in advance of the purchase.

10.6 Measurement Systems Analysis (MSA)

The identification and measurement of variation in the process are needed to determine if the system is performing as desired and if not, to provide insights into what must be better controlled in order to meet specifications. The purpose of measurement systems analysis is to measure, understand and control the variation caused by measurement systems. By separating out this source of variation, the impact of variation in the parameters or aspects being measured can be understood in relation to the cleaning method.

Before beginning a MSA it is extremely important:

- To clearly define the parameters or aspects to be controlled
- To identify tests capable of achieving the measurements needed
- To understand measurement requirements (bias, gage Repeatability and Reproducibility (R&R), accuracy, stability, linearity, etc.)

It can be very wasteful and stressful to achieve an unnecessarily low level of measurement sensitivity. For example, if lower limits of detection are quite good compared to the threshold level specification, then statistically significant differences between two tests, provided both are well below the threshold for acceptance, often have no operational significance. Be careful not to confuse the process of MSA for the overall goal: a safe and robust cleaning process that consistently meets its target values.

10.6.1 MSA Components

The measurement system variation for continuous data can be broken down into the sum of two components: R&R. Such studies examine the precision of a measurement system but not the accuracy.

Repeatability is an estimate of short term variation of the error that occurs when successive measurements are made under the same conditions.

Reproducibility is an estimate of the variation in the average of measurements made between operators using the same equipment or between laboratories performing the same assays and it captures the precision of the different groups (labs or operators).

10.6.2 Attribute R&R

Attribute R&R are used for discrete data often with binary outcomes and distributions (e.g., pass/fail, good/bad, yes/no). In these studies the focus is on analysis of the ability of the evaluator to detect nonconformance. This is called *effectiveness*. The effectiveness of different evaluators is compared when assessing reproducibility and how biased the evaluator is towards acceptance or rejection. The probability of false negatives/positives is also calculated, which results in the ability to measure bias towards one outcome or the other.

10.6.3 Minimizing Variations

There are guidelines for acceptable levels of variation for continuous data as well as attribute levels (effectiveness, bias (False Acceptance/Rejection)) ***(33)***. However the main goal is, as always, to achieve an acceptable level of control for the system in question based upon a previously agreed upon set of criteria that make sense from a business and patient safety perspective. Ideally, the bulk of the variation that one measures should come from the items being tested, not the test methods themselves.

Many actions can be taken to improve the precision of measurements.

- Regular maintenance and calibration of equipment
- Maintaining and updating SOPs
- Meaningful operator training
- Mapping or charting the process to identify sources of variation (noise)
- Alternative measurement systems for the aspect in focus
  - analytical method with greater resolution (discrimination)
  - development of better standards for comparison
  - ensure random sampling/test performance when collecting data
  - change from manual to automated system

10.6.4 MSA and Cleaning Validation Strategy

In cleaning validation carryover calculations, safety factors are always included in order to cover uncertainties due to cleaning as measured by visual inspection, assumptions about surface area, or the system in general. Sometimes one is faced with the dilemma of needing to have measurable limits and

thus being unable to apply the safety factor best practice would indicate. Within this framework of uncertainty, one must create a control strategy whose capabilities are sufficient to ensure patient safety.

MSA is a statistical tool that aids both the analytical methods of detection for carryover as well as the process parameters monitored in the control strategy for the cleaning process. Once the MSA for the analytic is under control, one can use the same MSA techniques to measure the variation within the control strategy. For example, one can answer the question about whether the pressure fluctuations measured at the spray ball are responsible for or correlated to the trends in TOC from rinse tests or is the variation simply due to the system used for pressure measurements? One can thus systematically address critical process parameters for better control. Should these investigations prove fruitless, then one must re-examine the assumptions in the risk assessments and control strategy that lead to the prioritization of these process parameters.

10.7 Cleaning for API Manufacture

Equipment for multiproduct intermediate and API manufacturing can be exposed to a large variety of substances and agents (e.g., solvents, reagents, catalysts, cell cultures and processing aids). Detailed written procedures should be established to enable effective and reproducible cleaning of these residues and subsequent release of the equipment for next use. Acceptance criteria for residues and the choice of cleaning procedures and cleaning agents should be justified on the basis of being practical, achievable and scientifically sound. For equipment producing later stage intermediates and final APIs, cleaning procedures will therefore need to be developed and validated to remove manufacturing residues that may include raw materials, un-isolated intermediates, by-products, degradants and the product itself. It should be noted that equipment used solely for some raw materials that are Generally Recognized as Safe (GRAS) and for raw materials or intermediates, visual inspection alone may be appropriate if all parts of the equipment are visually inspectable. For API manufacturing, lack of adequate cleaning may impact not only potential cross contamination of the next product, it may also impact the processing of the next product (e.g., if residual materials interfere with subsequent process reactions).

The need for limits for residual organic solvents should be evaluated and can utilize a risk assessment. For example, some residual organic solvents evaporate upon drying of the equipment. If there are measures in place (e.g., equipment drying or flush with next process solvent) that may mitigate the risk for residues of residual solvents then analytical limits may not be necessary. If necessary, limits for residual organic solvents may be derived from ICH Q3 guidance ***(19)***. Limits for other residues expected to be present after cleaning must also be established. For some residues, such as earlier intermediates, dose, toxicity, or acceptable daily intake information may not be established or available. For other residues, such as proteins or unstable residues, degradation may occur to produce multiple other residues, some of which may not be characterized. For these cases, other approaches to the establishment of limits may be necessary. Industry benchmarking data may be used to determine if there are common limits applied for these cases. For any limits approach used, the rationales and risk assessments used to establish that approach should be documented and approved.

Facilities and manufacturing systems for intermediates and APIs should be designed to facilitate cleaning as appropriate to the type and stage of manufacture. Equipment used for API manufacturing is often large, closed and complex. It often includes a significant amount of process piping and large-scale vessels, dryers, condensers and/or chromatography columns. For this reason, visual inspection of much of the equipment may not be possible due to inaccessibility. Equipment design for cleanability is a significant factor in the ease and reproducibility of cleaning for these types of large closed systems. Design factors of particular importance can include equipment and pipe sloping for drainage, elimination or minimization of deadlegs, adequate pump size for turbulent flow of cleaning solutions, and the use of spray coverage devices.

Quality risk-assessments should be used to determine the need for microbiological specifications (if any) after cleaning, if any. The harsh chemical environment (e.g., pH extremes, use of organic solvents, high temperature processes) that is often associated with small-molecule intermediate and API manufacture may eliminate the risk to product quality from microbiological proliferation. Where microbiological specifications have been established for the cleaning, facilities should be designed to limit exposure to objectionable microbiological contaminants. Equipment cleaning and/or sanitation studies should address microbiological and endotoxin contamination for those processes where there is a need to reduce total microbiological count or endotoxins in the API or other processes where such contamination could be of concern (e.g., aqueous-based processing of non-sterile APIs used to manufacture sterile products).

Cleaning validation at product changeover should be directed to situations or process steps where contamination or carryover of materials poses the greatest risk to API quality ***(34)***. Cleaning validation is typically performed on equipment used to produce later stage intermediates and APIs. See ICH Q7 Table 1 for guidance on where cleaning validation may be expected ***(34)***. For equipment used in early intermediate production, it may be unnecessary to validate equipment cleaning procedures. In these cases, cleaning verification for multipurpose equipment is still required. Validated analytical methods used to verify the equipment cleaning should be used. If product/processing residues are demonstrated to be removed by subsequent purification steps, this may be considered in a documented risk assessment to determine the level of cleaning and cleaning validation necessary.

Cleaning procedures should be monitored at appropriate intervals after validation to ensure that they remain effective when used during routine changeovers. Depending on equipment design and complexity, it is typical for API equipment cleanliness to be routinely monitored by analytical testing and/or visual examination, where feasible, after each cleaning after cleaning validation is completed. This is often associated with the higher risk of some API cleaning circumstances (e.g., large closed equipment that cannot be easily visually inspected and the fact that contamination of one batch of API can often implicate many batches of drug product). This routine cleaning monitoring after each campaign for multipurpose equipment is often accomplished via rinse sampling and testing for large closed equipment.

For more information on biotechnology API manufacture, see PDA Technical Report No. 49 ***(2)***.

10.8 Topical Drug Products

The major issue with topical drug products relates to how limits are set. The approach to setting limits depends on the systemic availability of the drug active ingredient when applied to the skin. Some topical products, such as drug patches, are actually transdermal delivery mechanisms to allow systemic availability of the drug active ingredients. While for other topical drug products, the effect of the drug active ingredient is limited to the skin itself and there is generally no, or very low, systemic availability of the drug active ingredient.

10.8.1 Topical Drug Products with Systemic Availability

Limits for topical drug products where the drug active ingredient is topically designed to be available systemically are established based on a typical carryover calculation based on a safe level in the next product. That safe level may be established on either a fraction of the dose or on a toxicological evaluation (see **Section 5.0**). A significant difference may be the portion of the active in the topical drug product that is systemically available from the cleaned topical product versus the portion of the active ingredient that is systemically available when that active ingredient is present as a residue in the next topical product. In the absence of specific information, it may be assumed as a worst case that the

residue of the cleaned active is 100% systemically available when in the next product. As with other carryover calculation based on the therapeutic dose, the minimum dose of cleaned active ingredient and the maximum dose of the next product should be adjusted based on factors such as the number of applications per day (or per other time period) and the amount of product applied per application.

Another factor that may be considered in setting limits in this situation is dermal irritation of the active ingredient. In most cases, this will not be a limiting factor, but it may be considered, particularly if the active ingredient, which is the residue, is not systemically available when present in the next topical drug product.

10.8.2 Topical Drug Products with No or Limited Systemic Availability

For some topical drug products, the therapeutic effect is limited to the skin to which the drug product is applied. An example of such a product is sunscreen (a drug product in some countries, such as the USA). If the therapeutic effect of the active ingredient is so limited then a modification of a traditional carryover calculation may be utilized. The reason is that a "dose" for such topical drug products is generally not well defined, as the "use instructions" may typically read "Apply to the affected area."

10.8.2.1 Adjusted Calculation

A traditional carryover calculation bases the limit on a minimum dose of active ingredient of the product that is cleaned and a maximum dose of the next drug product. However, in this situation (where the effect of the active ingredient is limited to the skin it is applied to) it is not necessary to consider the minimum dose of the cleaned active ingredient as application to a very small area (such as 100 cm^2) and the maximum dose of the next product as application to the entire body (such as 1.6 m^2). Those calculations can be used but they result in extremely low limits. However, the relevant safety concern is what happens if 0.001 of the amount of active applied to a given area (such as 100 cm^2) appears in the next drug product which is also applied to the same surface area (in this example, 100 cm^2). Because the therapeutic effect is limited to the skin surface the drug product is applied to, limits can be based on 0.001 of the concentration of the active ingredient from the cleaned product in the subsequently manufacture drug product (suitably modified by application conditions which will be discussed shortly). In other words, if the drug product which is cleaned contains 0.5% drug active ingredient, then the safe level *in the next drug product* is 0.001 of that concentration, or 0.0005% (5 ppm).

10.8.2.2 Modification Based on Frequency of Application

Carryover calculations should be modified first based on the frequency of application. For example, if the cleaned product is applied a minimum of once per day and the second product is applied a maximum of three times a day, then the limit should be lower by a factor of 3 (with a resulting limit of 0.00016% in the example given). If the first product is applied a minimum of three times a day and the second product applied a maximum of once per day, then the limit may be higher by a factor of 3 (resulting in a limit of 0.0015% in the example given).

10.8.2.3 Modification Based on Amount Applied per Surface Area

A second modifying factor is based on the amount applied per surface area. This is sometimes difficult to assess. However, if it is clear that one product is applied at a significantly higher amount per surface area then that factor should also be considered. For example, if the cleaned product is typically applied at a rate of 2 mg/cm^2 and the second product typically applied at a rate of 4 mg/cm^2, the concentration limit in the basic example given would be lower by a factor of 2 (resulting in a concentration limit of 0.00025%).

One approach is to establish a therapeutic dose of topical preparation in terms of area of application covered by one fingertip unit (FTU), which is defined as the amount of topical preparationointment

dosadelivered from a tube with a 5-mm diameter nozzle, applied from the distal skin-crease to the tip of index finger an adult forefinger ***(35).*** One FTU measures approximately 0.5g. As the average human adult area covered by 1 FTU is 286 cm^2, approximately 1.75 mg of the topical formulation is applied per each square centimeter of the skin surface area.

10.8.2.4 Additional Considerations

If a firm has a policy or procedure for a default limit (such as 10 ppm of the cleaning active in the next drug product), then the calculated limit (considering the modification discussed in **Sections 10.8.2.2** and **10.8.2.*3***) should be compared to that default limit and the lower of the two values utilized for subsequent calculations.

In addition, if there is evidence that the active ingredient in the cleaned product would be systemically available if it were present in the vehicle (excipients) of the next product, then the calculation in 10.8.1 may not be applicable. In such a case, either the calculation in 10.8.1 should be considered or the order of manufacture may be restricted.

10.8.3 Additional Safety Considerations

If active ingredients used in topical preparations produce adverse skin irritation effects, hypersensitivity, and/or possible photosensitivity reactions, those considerations should be evaluated to determine whether more stringent residue limits should be established.

10.8.4 Additional Cleaning Considerations

Topical drug products may present cleaning challenges because of the nature of the excipients used and the high viscosities of the drug product. In place of a water prerinse, it may be necessary to physically remove gross amounts of product left on equipment surfaces using a plastic scraper or a nonwoven wipe. Particularly if the excipients are designed to make the topical drug product "waterproof", more stringent cleaning process conditions, such as higher temperatures or higher concentrations of cleaning agents, may be required for effective cleaning.

10.9 Animal Drug Products

Cleaning validation for animal drug products is basically the same as for human drug products. The main complication is in setting limits because one product (the cleaned product) may be for one animal species and the next product manufactured in the cleaned equipment may be for a different species. For example, the cleaned product may be dosed only to horses and the next product dosed only to dogs. In this situation, a toxicological assessment to determine a safe limit should be considered for the effect of the active ingredient of the cleaned product (dosed only to horses) as if it were used for dogs. All relevant toxicology and safety information should be considered; for example, drugs that may be residues in products for cows may have restrictions not based on toxicity to the cows but because of concerns about safety of the cow's milk. These concerns may also apply to facilities that make both human and animal drugs. Limits based on toxicological evaluations are discussed in **Section 5.0.**

10.10 Packaging Components and Packaging Equipment

10.10.1 Primary Packaging Components

Product contact surface of primary packaging closures and containers should be free of materials that could adulterate the drug product to the extent that fitness for use would be compromised. An evaluation of suitability may include considerations of manufacturing process residues, cleaning agents/solvents, particles, bioburden and/or endotoxin.

10.10.1.1 Oral Dosage Forms Primary Packaging Components

Cleaning of containers and stoppers used for oral dosage forms is based on a risk analysis. The risk should be assessed and appropriate cleaning levels defined that will control the risks to acceptable levels. Cleaning of containers for solid oral dosage forms, related to risk analysis, could be limited to removing of solid material by blowing a stream of compressed filtered air into the bottles while inverted. From a microbial perspective, most solid oral drug products will not allow microorganisms to proliferate, due to the extremely low water activities of these types of products.

Some consideration could be provided for the cleaning of containers for liquid oral dosage forms even if the liquid does inhibit growth of microorganisms, due to presence of components, like preservatives or sugar at high concentrations, or a final terminal heat treatment.

10.10.1.2 Parenteral Dosage Forms Primary Packaging Components

Cleaning of containers and stoppers used for parenteral dosage forms is based on a risk analysis. The risk should be assessed and the cleaning levels validated at the acceptance criteria. Since the parenteral container/closure components are in contact with the drug product, similar cleaning qualification considerations as for direct product contact surfaces for manufacturing equipment should be addressed.

For cleaning processes used as a depyrogenation step for container/closure components, the qualification should demonstrate successful endotoxin removal ***(36).*** The efficiency of the cleaning process to depyrogenate can be assessed by spiking containers or closures with known quantities of endotoxin, followed by measuring endotoxin content after cleaning. The studies are typically performed by applying a reconstituted endotoxin solution onto the test surfaces and allowing the solution to air dry. Positive controls (test surfaces with applied endotoxin but without the endotoxin reduction process) should be used to measure the percentage recovery in the test method. Data should demonstrate that the cleaning process reduces the endotoxin content by at least a 3-log reduction in a spiking study.

Container washer qualification should start by using a spray coverage test to verify all the surfaces are efficiently rinsed. The cleaning performance qualification should consider removal of residues coming from the surface treatment (if applicable) and/or particles (which, as an example, could come from burned glass molding lubricant as well as glass particles if breakage occurs before wash).

For closures (such as stoppers), the cleaning performance qualification should consider removal of residues coming from the closure manufacturing process, like the lubricant and cleaning agent used, as well as particles.

10.10.2 Packaging Equipment

Packaging equipment may be categorized into primary and secondary equipment.

10.10.2.1 Primary Packaging Equipment

Primary packaging equipment may exert direct impact on the quality of the finished product. Examples of such equipment may include oral, topical and aseptic liquid fillers, tablet fillers, oral powder fillers, tube fillers, blister machines and other filling machinery that has parts with direct finished dosage product contact. The cleaning processes and validation practices for primary equipment should not differ from the same practices utilized for direct impact manufacturing equipment as they present similar risk of cross contamination. Auxiliary equipment such as hoppers, tubing, piping, conveyors, cappers, cottoners and other product contact surfaces should be cleaned and validated the same as associated filling equipment. The design of packaging equipment should consider "gentle handling" of finished product to minimize possible attrition and breakage in the case of solid dosage products and possible adsorption of liquids. The

cleaning of dedicated primary packaging lines may not require validation. Consideration should be given to design of the lines and cleaning procedures to minimize validation efforts. While there is a possibility of preferential transfer of residues from the primary packaging equipment to an initial portion of the packaged product, this risk may be reduced by discarding an initial portion of processed product.

10.10.2.2 Secondary Packaging Equipment

Secondary packaging equipment, such as induction sealers, retorquers, labelers, palletizers and other similar equipment that does not have direct impact on the quality of the product, should be designed to allow only minimal inevitable residuals generated by the packaging process. However, appropriate attention should be given to document cleaning of this secondary equipment.

Once the drug substance is sealed in its primary packaging, the risk of cross-contamination is generally relatively low. Cleaning processes should be used on the packaging lines after primary packaging, but do not require cleaning validation. The main concern with cross-contamination is a compromised primary package (such as a broken vial or a crushed bottle) that might release product that transfers to the outside of the primary packaging of a different product. Depending on the hazard properties of the product, its presence on the outside of the primary packaging of a different drug product may be an unacceptable risk. Cleaning processes for such situations should be considered. However, because contamination of the next product may only involve contamination of the outside of the primary package, the requirements for cleaning validation should be assessed based on risk to patients or to people handling the vials from that external contamination on the primary package. In those cases where the risk is significant (such as a genotoxic API), a dedicated line or a cleaning step known to remove, deactivate or degrade that active drug should be considered. Degradation processes may appropriately be confirmed in a laboratory study demonstrating degradation or inactivation of the highly hazardous API.

10.11 Tubing and Hoses

Tubing and hoses have diverse transfer applications in pharmaceutical manufacturing operations. Types may vary from flexible plastics to fixed stainless steel piping. Conditions for use may be single- or multiple-use. Biocompatibility and inertness of the tubing with the contact material is a primary consideration prior to use. The regulatory standards on transfer tubing and hoses used in manufacturing processes are covered under compliance with U.S. FDA standards 21 CFR Part 177.2600 ***(37)***. This rule is applied in combination with ISO 10993-1 ***(38)*** standard for medical devices and USP class I-VI plastics tests ***(39)*.**

The procedure for cleaning should be effective for exposing all product contact surfaces and the internal bore of tubing to the cleaning detergent and rinsing solution or water. A key for cleaning of tubing and hoses is to assure turbulent flow throughout as well as to assure proper sloping for drainage for fixed tubing. Visual inspection of the internal bore of the tubing/hose to evaluate the efficiency for removal of residue may be performed with the aid of video devices, such as a borescope. It is recommended to drain tubing and hoses of any water/resident solution *when* not in use. Tubing/hoses cleaned in place attached to the main equipment receive the same cleaning regimen as the equipment. Although priority is given to the attached equipment when selecting the cleaning detergent and procedure, evaluation of the impact on the cleaning and storage (hold time) conditions of tubing/hoses should be considered. Shorter tubing length may benefit cleaning ability, drainage and storage management. CIP cleaning equipment or automated hose washers often may be utilized and qualified to consistently perform cleaning of tubing or hoses.

Design of the tubing and hoses should take into consideration welded or permanently embedded

fittings for ease of cleaning. If removable end fittings are used, they should be removed during each cleaning cycle. If not dried before storage, tubing/hose should be stored on the slope (to allow drainage) and should be covered using hose-end covers of spun-bonded polyolefin or similar materials to reduce the risk of microbial and/or particulate contamination during storage.

Based on the material of composition, the indicators of damage (such as pressure testing) should be predefined for the tubing under the conditions of use. Qualification for use of product contact tubing and hoses should include an assessment of the useful lifetime for the manufacturing operation. The assessment should integrate a visual component of inspecting tubing periodically for signs of tear, pitting and disintegration, with wear characteristics, such as particulate shedding detected under subvisible conditions.

10.12 Excipients

The excipients used for a drug product should be considered in the cleaning validation program. One issue for excipients is the possible effect on cleaning of a drug product. This effect is generally more pronounced for solid dosage products, where the excipient may be a coating or other functional material designed to retard dissolution. This is one reason why some companies prefer to use a laboratory cleaning study, as compared to only evaluating the solubility of the active ingredient, to determine the difficulty of cleaning of different products in a grouping approach.

Unless the excipient has some kind of unusual toxicity, limits are generally not set for excipients in a cleaning validation protocol. A case where limits may be set for excipients is where the excipient is known to have a significant effect on the performance of the next manufactured product, such as complexing with the API to reduce bioavailability. However, it should be recognized that in all cases, residues of excipients after cleaning should be such that the equipment is visually clean. A surface which is not "visually clean" due to a high level of an excipient should be generally considered a cleaning validation failure.

10.13 Dedicated Equipment

Equipment for pharmaceutical manufacturing and packaging may be dedicated for processing only one product. Some points to consider regarding cleaning validation of dedicated equipment are covered below.

10.13.1 Reasons for Dedication

Reasons for dedication of equipment may be quality driven (such as to avoid cross-contamination of one active ingredient into another product) or may be based on business considerations (such as for production efficiency). Regulatory agencies recommend dedicated equipment and/or facilities in certain situations. For example, the PIC/S recommendations state that "Dedicated equipment should be used for products which are difficult to remove (e.g., tarry or gummy residues in bulk API manufacturing), for equipment which is difficult to clean (e.g., bags for fluid bed dryers), or for products with a high safety risk (e.g., biological or products of high potency which may be difficult to detect below an acceptable limit)" ***(22)***. That PIC/S document also states that "For certain allergenic ingredients, penicillins, cephalosporins or potent steroids and cytotoxics, the limit should be below the limit of detection by best available analytical methods. In practice this may mean that dedicated plants are used for these products." Additionally, the ANVISA Resolution – RDC No. 17 states that "There should be used segregated facilities and dedicated to the production of certain medications such as certain biological preparations (e.g., live microorganisms) and the highly sensitizing materials (e.g., penicillin, cephalosporin, carbapenem and other beta-lactic derivatives) in order to minimize the risk of serious

damage to health due to cross contamination", and further that "The production of certain highly active products, such as some antibiotics, certain hormones, cytotoxic substances should be held in segregated areas" ***(40).*** Finally, there are the U.S. FDA draft recommendations about dedication for beta-lactams ***(41).***

Risk assessments and appropriate controls should be considered in cases where regulatory documents may be unclear or overly strict on the requirement for dedication or segregation for manufacturing.

10.13.2 Cleaning Validation Issues

Since cross-contamination of the active ingredient from the previous product to the next product is not an issue for dedicated equipment, cleaning validation related to the active itself is generally not considered a requirement. The 1993 U.S. FDA cleaning validation guidance states that "When the cleaning process is used only between batches of the same product (or different lots of the same intermediate in a bulk process) the firm need only meet a criteria of, "visibly clean" for the equipment. Such between batch cleaning processes do not require validation" ***(20)***. Since "between batches of the same product" may refer to dedicated equipment and/or a campaign between products, it can be interpreted that cleaning validation is not required for these scenarios. However, cleaning validation should be considered for dedicated equipment if carryover of the cleaning agent or the contribution of bioburden or degradation byproducts to the next manufactured batch is a concern. In its Compliance Guidance Manual 7356_002, U.S. FDA clarified their position by stating that "lack of demonstration of effectiveness of cleaning" for dedicated equipment warrants a warning letter ***(42)***. It makes good sense for manufacturers to conduct risk assessments for all cleaning scenarios to determine the need for cleaning validation to comply with product quality (including residues and lot integrity) and regulatory expectations. Principles for determining acceptance criteria for cleaning agent, bioburden, endotoxin, and degradation products for cleaning validation of dedicated equipment are essentially the same as for nondedicated equipment. It is considered to be best practice to document effectiveness of a cleaning process for dedicated equipment even if "visually clean" is the only criteria.

11.0 Regulatory and Guidance Documents

Cleaning validation is required by regulatory authorities worldwide. It is encapsulated in the U.S. CGMPs ***(6,43)*** and in the EU GMPs ***(22,44).*** ICH Q7 also stresses the importance of cleaning validation for API manufacture ***(36).*** FDA, PIC/S and WHO also require cleaning validation in guidances ***(20,22,45).*** There are other guidance documents from various countries but most are a variation on the U.S. FDA guidance and/or the PIC/S recommendations. It is recommended that the applicable regulations and guidances be carefully consulted as part of the design or evaluation of a cleaning validation program.

12.0 References

1. *Technical Report No. 29*: *Points to Consider for Cleaning Validation;* Parenteral Drug Association: 1998.
2. *Technical Report No. 49*: *Points to Consider for Biotechnology Cleaning Validation;* Parenteral Drug Association: 2010.
3. Quality Guideline Q8(R2): *Pharmaceutical Development;* International Conference on Harmonisation: 2009. www.ich.org.
4. Quality Guideline Q9: *Quality Risk Management*; International Conference on Harmonisation: 2005. www.ich.org.
5. Quality Guideline Q10: *Pharmaceutical Quality Systems*; International Conference on Harmonisation: 2008. www.ich.org
6. U.S. Code of Federal Regulations, *Title* 21 Part 211: *Current Good Manufacturing Practice for Finished Pharmaceuticals*. www.ecfr.gpoaccess.gov.
7. *Note for Guidance on the Quality of Water for Pharmaceutical Use*; EMEA: 2002.
8. Rathore, N.; Qi, W.; Chen, C.; Ji, W. Bench-Scale Characterization of Cleaning Process Design Space for Biopharmaceuticals. *BioPharm Internat.* **2009,** *22*, 32-45.
9. U.S. Food and Drug Administration, Center for Drug Evaluation and Research *Press Release. U.S. FDA Takes First Step in Recognizing the Role of Emerging Technologies in the Area of Process Validation;* 2004 (March). http://www.cleaningvalidation.com/Resources/Press%20release%203%20val%20runs%20March%202004.pdf .
10. *Guidance for Industry: Process Validation: General Principles and Practices*; U.S. Food and Drug Administration: 2011.
11. *Guidance for Industry: SUPAC-IR/MR: Immediate Release and Modified Release Solid Oral Dosage Forms Manufacturing Equipment Addendum, CMC 9;* U.S. Food and Drug Administration: 1999.
12. *Baseline Guide: Risk-Based Manufacture of Pharmaceutical Products (Risk-MaPP)*, First Edition; ISPE: 2010.
13. Conine, D.L.; Naumann, B.D.; Hecker, L.H. *Setting Health-Based Residue Limits for Contaminants in Pharmaceuticals and Medical Devices*. *Qual. Assur.* **1992**, *1*(3), 171-180.
14. Kramer, H.J.; van den Ham, W.A.; Slob, W.; Pieters, M.N. Conversion Factors Estimating Indicative Chronic No-Observed-Adverse-Effect Levels from Short-Term Toxicity Data. *Reg. Tox.Pharmacol.* **1996,** *23*, 249-255.
15. Layton, D.B.; et al. Deriving Allowable Daily Intakes for Systemic Toxicants Lacking Chronic Toxicity Data. *Reg. Tox. Pharmacol.* **1987**, *7,* 96-112.
16. *Guidance on the Limits of Genotoxic Impurities*; EMEA: 2006.
17. LeBlanc, D.A. PDA Survey Results: Cleaning Validation Sampling Practices. *PDA Letter.* **2008,** *44*(10), 11-15.
18. *Guidance on aspects of cleaning validation in active pharmaceutical ingredient plants*; CEFIC: 2000. http://apic.cefic.org/pub/pub-cleaning-validation.pdf (accessed January 26, 2012).
19. Quality Guideline Q3C(R5): *Impurities: Guideline for Residual Solvents*; International Conference on Harmonisation: 2011. www.ich.org.
20. *Guide to Inspections of Validation of Cleaning Practices*; U.S. Food and Drug Administration: 1993. www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074922.htm (accessed Dec. 20, 2012).
21. Guide-0028: *Cleaning Validation Guidelines*; Health Canada: 2008. www.hc-sc.gc.ca/dhp-mps/compliconform/gmp-bpf/validation/gui-0028_cleaning-nettoyage_ltr-doc-eng.php (accessed Dec. 20, 2012).
22. PI 006-3 PIC/S Guide: *Recommendations on Validation Master Plan, Installation and Operational Qualification, Non-Sterile Process Validation Cleaning Validation;* Pharmaceutical Inspection Convention (Scheme): 2007. www.picscheme.org (accessed Dec. 20, 2012).
23. Fourman, G.L.;Mullen, M.V. Determining Cleaning Validation Acceptance Limits for Pharmaceutical Manufacturing Operations. *Pharm. Technol.* **1993**, *17*, 54-60.
24. Questions and Answers on Current Good Manufacturing Practices, Good Guidance Practices, Level 2 Guidance Equipment Question 2; U.S. Food and Drug Administration: 2005. http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124777.htm (accessed Dec. 20, 2012).
25. LeBlanc, D.A. PDA Survey on Analytical Methods for Cleaning Validation. *PDA Letter.* **2007**, *43*(10),16-18.
26. LeBlanc, D.A. *Cleaning Validation: Practical Compliance Solutions for Pharmaceutical Manufacturing,* Vol. I*;* Parenteral Drug Association/DHi: 2006, 191-194. www.pda.org/bookstore.
27. Mehta, N.K. Development of an In Situ Spectroscopic Method for Cleaning Validation Using Mid-IR Fiber-Optics. *Biopharm Internat.* **2002,** *15*, 36-42.
28. *Technical Report No. 33: Evaluation, Validation and Implementation of New Microbiological Testing Methods*; Parenteral Drug Association: 2000. www.pda.org/bookstore.

29. Quality Guideline Q2(R1): *Validation of Analytical Procedures: Text and Methodology*; International Conference on Harmonisation: 2005. www.ich.org

30. General Chapter <1227> Validation of Microbial Recovery from Pharmacopeial Articles. *USP 34/NF 29;* U. S. Pharmacopeia: 2011. www.usp.org

31. Torbeck, L.D. Statistical Solutions: %RSD: Friend or Foe. *Pharm. Tech.* **2010**, *34*, 37-38.

32. *Guidance for Industry: PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing and Quality Assurance*; U.S. Food and Drug Administration: 2004. www.fda.gov/downloads/Drugs/.../Guidances/ucm070305.pdf (accessed Dec. 20, 2012).

33. *Measurement Systems Analysis*; 4th edition, Automotive Industry Action Group: Michigan, 2010. www.aiag.org (accessed Dec. 20, 2012).

34. Quality Guideline Q7: *Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients*; International Conference on Harmonisation: 2000. www.ich.org.

35. Long C.C.; Finlay, A.Y. The fingertip unit: a new practical measure. *Clin. Exper. Dermatol.* **1991**, *16*, 444-446.

36. *Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing -- Current Good Manufacturing Practice*; U.S. Food and Drug Administration: 2004. http://www.fda.gov/downloads/Drugs/.../Guidances/ucm070342.pdf (accessed Dec. 20, 2012).

37. U.S. Code of Federal Regulations, Title 21 Part 177.2600: Indirect Food Additives: Polymers, Articles Intended for Repeated Use; www.ecfr.gpoaccess.gov.

38. ISO 10993-1:2009: Biological evaluation of medical devices Part 1: Evaluation and testing in the risk management process; International Organization for Standardization: 2009. www.iso.org.

39. General Chapter <88> Biological Reactivity Tests, In Vivo. *USP34/NF29* U. S. Pharmacopeia: 2011. www.usp.org

40. RDC no. 17: *Technical Regulation of Good Manufacturing Practices of Drugs*; ANVISA: www.rx-360.org/LinkClick.aspx?fileticket=yvGoEzQimQc%3D&tabid=38. (accessed Nov. 29, 2011).

41. *Draft Guidance for Industry: Non-Penicillin Beta-Lactam Risk Assessment: A CGMP Framework;* U.S. Food and Drug Administration: 2011. http://www.fda.gov/downloads/Drugs/.../Guidances/UCM246958.pdf (accessed Dec. 20, 2011).

42. *Compliance Program Guidance Manual for FDA Staff: Drug Manufacturing Inspections Program 7356.002;* U.S. Food and Drug Administration: 2002. http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm095598.htm

43. U.S. Code of Federal Regulations, Title 21 Part 210: Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drug; General. www.ecfr.gpoaccess.gov.

44. *Qualification and Validation: Final Version of Annex 15 to the EU Guide to Good Manufacturing Practice*. European Commission Enterprise Directorate: Working Party on Control of Medicines and Inspections: 2001. http://ec.europa.eu/health/files/eudralex/vol-4/pdfs-en/v4an15_en.pdf (accessed 21 March 2011).

45. Appendix 3 of Annex 4, Supplementary Guidelines on Good Manufacturing Practices: Validation, WHO Technical Report Series 937: World Health Organization: 2006.

13.0 Suggested Readings

Note that these readings are in addition to the various footnoted references specific to a given topic.

1. *Bioprocessing Equipment (BPE) Standard*; American Society of Mechanical Engineers: **2009.**
2. E2500-07: *Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment*; American Society for Testing and Materials: 2007.
3. E2363 - 06a: *Standard Terminology Relating to Process Analytical Technology in the Pharmaceutical Industry*, American Society for Testing and Materials: 2006.
4. E2537-08; *Standard Guide for Application of Continuous Quality Verification to Pharmaceutical and Biopharmaceutical Manufacturing*, American Society for Testing and Materials: 2008.
5. Bismuth, G.; Neumann, S. *Cleaning Validation: A Practical Approach*; Interpharm Press: Colorado, 1999.
6. EudraLex, *EU Guide to Good Manufacturing Practice, Volume 4 Annex 15, Qualification and Validation;* European Commission: 2001.
7. Laban, F. et. al. Validation of Cleaning Processes: Report of a SFSTP Commission. *S.T.P. Pharma Pratiques.* **1996**, *6*, 5-40.
8. LeBlanc, D.A. PDA Survey Sheds Light on Current Practices in Setting Residue Limits. *PDA Letter.* **2007**, *43*(5),11-14.
9. LeBlanc, D.A. PDA Survey Results: Cleaning Validation Sampling Recovery Practices, *PDA Lett*. **2009,** *45*(7), 9-15.
10. LeBlanc, D.A. *Validated Cleaning Technologies for Pharmaceutical Manufacturing*; Interpharm Press: Colorado, 2000.
11. LeBlanc, D.A. *Cleaning Validation: Practical Compliance Solutions for Pharmaceutical Manufacturing, Vol. II*. PDA/DHI: 2010. www.pda.org/bookstore.
12. *Pharmaceutical CGMPs For The 21st Century – A Risk-Based Approach: Final Report;* U.S. Food and Drug Administration, U.S. Government Printing Office: Washington, DC, 2004.
13. *Cleaning and Cleaning Validation: Volume I*; Pluta, P.L. (ed.); Parenteral Drug Association/DHI: 2009. www.pda.org/bookstore.
14. Verghese, G. *Selection of Cleaning Agents and Parameters for cGMP Processes* in Proceedings of the INTERPHEX Conference, Philadelphia, PA, March 17-19, 1998.

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