Validation for Pharmaceutical Industry

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Why Validation?

I. INTRODUCTION

The prime objective of anyone working in a pharmaceutical plant, whether in production or quality control, is to manufacture products of the requisite quality at the lowest possible cost. In this chapter it will be shown_ that proc-ess validation is essential for the achievement of this objective.

In June 1980, Theodore Byers defined validation as follows: "Validation is attaining and documentation of sufficient evidence to give reasonable assur-ance, given the current state of science, that the process under consideration does, and/or will do, what it purports to do."

There are three reasons why the pharmaceutical industry is concerned that their processes perform consistently as expected:

government regu-lation;

assurance of quality; and

cost reduction.

Government Regulation: The United States, Food and Drug Administration, current Good Manufacturing Practices (GMPs) do not talk specifically about process validation, but the concept of validation is strongly implied through-out the document. Moreover, the concept of Good Manufacturing Prac-tices is meaningless without process validation.

Such control procedures shall be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product.

Valid in-process specifications for such characteristics shall be con-sistent with drug product final specifications and shall be derived from previous acceptable process average and process variability estimates where possible and determined by the application of suitable statistical procedures where appropriate.

Appropriate written procedures, designed to prevent objectionable micro-organisms in drug products not required to be sterile, shall be established and followed.

Assurance of Quality*:* Without process validation, which implies a proc-ess that is well understood and in a state of control, confidence in the qual-ity of products manufactured is impossible. GMPs and Process Validation, two concepts that cannot be separated, are essential to quality assurance. Frequently, the validation of a process will lead to quality improvement, in addition to better quality consistency.

Cost Reduction*:* Experience and common sense indicate that a validated process is a more efficient process and a process that produces less reworks, rejects, wastage, etc. Process validation is fundamentally good business practice. Although compliance with government regulations is important, the principal reason for validating a process is assurance of quality at a reduced cost.

The term "**validation**" is a relative newcomer to the lexicon of the phar-maceutical industry. On the other hand, the concept of validation is not new to the pharmaceutical industry, since it has been validating processes for many years:

All of us have validated our processes to some extent. It would not be economically feasible to

use equipment not knowing if it will produce the product we want, not to employ people with no assurance that they can do the job, nor fail to implement in-process checks or examinations to assure that products meet specifications.

Although validation studies have been conducted in the pharmaceutical industry for a long time, there is an ever-increasing interest in process validation due to the industry's greater emphasis in recent years on quality assurance and productivity improvement. Process validation is a necessary part of a quality assurance program and fundamental to an efficient produc-tion operation.

Furthermore, the limitations of end-product testing to assure quality have become more clearly understood. The performance of sterility testing, 100% inspection for particulates, assay for the active ingredient, etc., cannot guarantee that each unit of the product meets specifications. Thus, the heavy emphasis on quality assurance, good manufacturing practices, "build-ing quality in," and in-process control, all of which imply and require that processes be validated.

The pharmaceutical industry uses expensive materials, sophisticated facilities and equipment, and highly qualified personnel. The efficient use of these resources is necessary for the continued success of the pharmaceu-tical industry. The cost of product failures-rejects, reworks, recalls, complaints, etc.--is a significant part of the total production cost. Detailed study and control of the manufacturing process-validation-is necessary if failure costs are to be reduced and productivity improved.

II. DEFINITIONS

There have been many definitions of validation proposed, but at the present time there is no universally accepted definition. The definition given at the beginning of this chapter is excellent and widely used. For the purposes of this chapter a precise definition is not critical. It is intended that the reader of this chapter and of this book will obtain thereby a practical, work-ing understanding of validation. Two additional, frequently used terms in the process validation literature are "qualification" and "challenge." Since there is confusion in terminology, the sense in which validation, qualification, and challenge are used in this chapter will be defined and described.

Process Validation*:* Process Validation is the scientific study of a process:

- To prove that the process is doing what it is supposed to do, i.e., that the process is under control
- To determine the process variables and acceptable limits for these variables, and to set up appropriate in-process controls

Process optimization-to optimizes the process for maximum efficiency while maintaining quality standards-is a natural consequence of this scientific study of process variables and their control.

Validation lends itself to a variety of approaches. Two commonly used approaches are the review of historical data and a system challenge. Fre-quently a combination of these two is used. Also, there are acceptable variations within these two basic approaches. On occasion, there is no appropriate challenge test and, if the process is new, no historical data. In this case one studies the system design, tests the output of the system, in-stalls appropriate controls, and monitors the system. An example of such a case is a Water-for-Injection system [4].

Validation essentially involves a determination of the critical variables and the acceptable range of these variables, followed by the continuous con-trol of these variables. There are numerous ways to accomplish these objectives.

***Qualification**:* "the performance of tests to determine if a component of a manufacturing process possesses the attributes required to obtain a specified quality of a product" [5].

Qualification deals with components or elements of a process, while val-idation deals with an entire manufacturing process for a product (see Fig. 1). In Section III of this chapter some of the typical components of a process are described.

***Challenge**:* "the performance of tests to determine the limits of capability for a component of a manufacturing process. Limits of capability do not necessarily mean challenging until destruction, but limits of variation within which a defined level of quality can be assured" [5].

III. COMPONENTS OF VALIDATION

The validation of a process requires the qualification of each of the important elements of that process. The relative importance of an element may vary

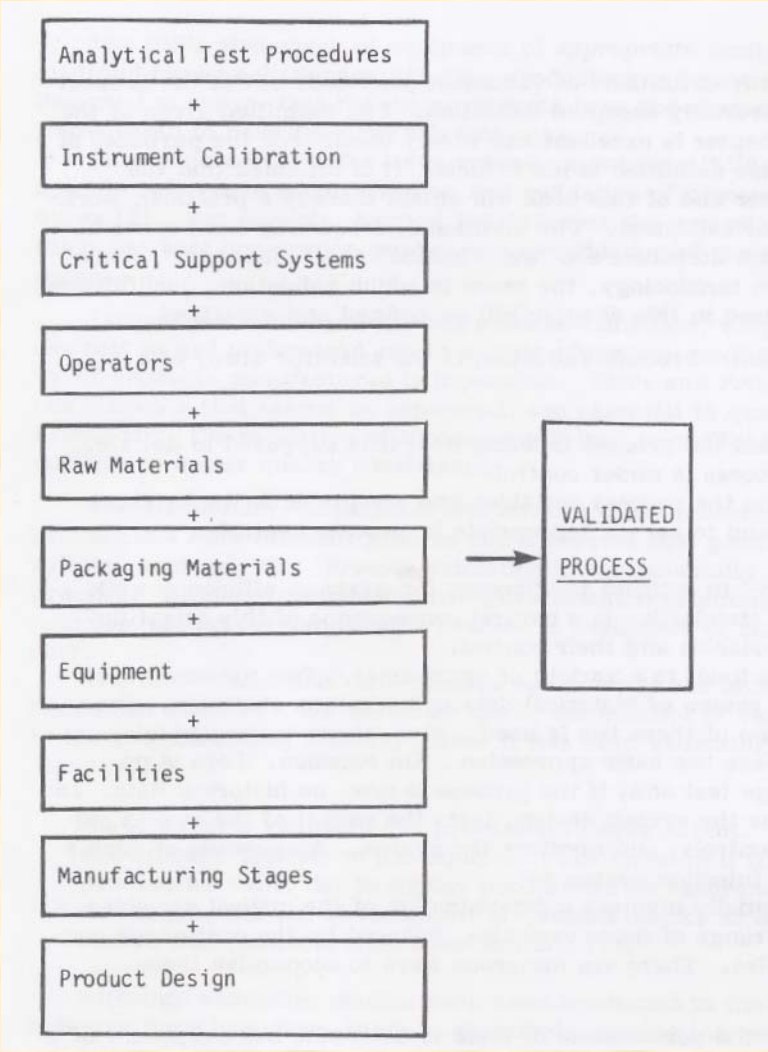

FIGURE 1 Qualification of each of the components of a process results in a validated process.

From process to process. Some of the components commonly considered in a process validation study include:

A] Analytical test procedures
B] Instrument calibration
C] Critical support systems
D] Operator qualification
E] Raw and packaging materials
F] Equipment
G] Facilities
H] Manufacturing stages
I] Product design

A. Analytical Test Procedures

Analytical test procedures are used to determine potency of the active ingre-dient, levels of impurities or degradation products, etc. The qualification of an analytical test procedure requires demonstration of suitable accuracy, precision, specificity, sensitivity, and ruggedness of the method. Criteria of suitability depend on the purpose of the method. The assay of a potent active ingredient must be more precise and more accurate than the determi-nation of a nontoxic degradation product. Since analytical test procedures are used in the qualification of other components of the process, their qualification is one of the first tasks performed.

B. Instrument Calibration

A pharmaceutical process uses many measuring devices to control the process. This control is accomplished either automatically by an appropriate feedback mechanism or through manual adjustments by an operator. In either case, the proper calibration of the measuring device is critical to the process. Some devices that need calibration are thermometers, pressure gauges, relative humidity meters, conductivity meters, timers, alarms, etc.

Calibration can be defined as the comparison of a measurement standard or instrument of known accuracy with another standard or instrument to detect, correlate, report, and/or eliminate by adjustment any variation in accuracy of the item being compared.

Validation means controlling the variables. One variable is equipment instrument, and measuring device accuracy. This variable is controlled through calibration. Some laboratory instruments that need to be calibrated are balances, spectrophotometers, chromatographs, calculators, computer; pH meters, rheometers, etc.

Before further validation studies can be attempted, the dependability and accuracy of the equipment used to monitor, control, and evaluate the process must be assured. Thus calibration is carried out early in the validation program. The specifications and frequency of calibration must be related to the use of the device or instrument in the context of the overall process. (Metrology will be discussed in a later chapter.)

C. Critical Support Systems

A support system is any general system that the plant needs to operate daily. These include air systems, electrical network, vacuum for cleaning, water supply and others. For purposes of validation we are concerned with critical support systems. These are systems that must operate at a certain level in order to maintain the required level of quality of the final product. It is evident, for example, that inadequate air filtration could result in a contaminated product, especially when performing an aseptic fill.

Some examples of critical support systems are

HVAC- heating, ventilation, and air conditioning

Water- water for Injection, Purified Water, Potable water

Steam
Compressed air
Nitrogen
Drainage system

The qualification of a critical plant support system consists of three phases:
Design
Installation and challenge
Monitoring

Designing the system, or for an existing system defining it, is the first phase. Technical data on system components (filters, deionizers, compres-sors, valves, etc.) must be located, reviewed, and collated. Distribution drawings of the HVAC, water, and drainage systems have to be prepared. While defining an existing system, it is likely that system deficiencies will be identified that must be corrected (plumbing dead legs, incorrect pressure gradients, inadequate filtration, etc.). The second phase involves making sure that the installed system performs as designed and, if possible, challenging the system to make sure that for normal and reasonable inputs the system output is acceptable. Finally, the system must be monitored at regu-lar intervals to make sure that it continues to function properly. For example, a HEPA filter is usually challenged using the standard DOP test and fre-quently monitored for leaks with a particle counter**.**

D. Operator Qualification

The operation is the most important component in a process. Thus the qual-ification of the operator by training and experience is absolutely essential to the success of the whole validation program. An untrained operator can negate the work done in qualifying the other components of the process. The qualified operator is trained in all aspects of the job--technical, supervisory, productivity, good manufacturing practices, etc.

It is important in the train-ing program to emphasize the necessity of not making changes in a validated process without considering the consequences of the change, such as the need to revalidate the process if the change is significant. Frequently, the problems and failures that occur are caused by changes made in a thoroughly studied, validated system, by well-intentioned personnel.

E. Raw Materials and Packaging Materials

Qualification of materials involves the setting of specifications for all critical parameters of these materials. These specifications must be set in light of their purpose in the product and the end use of the product. Frequently the materials will have specifications in addition to those found in an official pharmacopeia, such as a particle size specification for an ingredient in a suspension formulation. Second, vendors must be qualified. Vendor qual-ification usually includes testing of samples and an audit of the vendor's facilities.

For a parenteral product, the container /closure system is especially im-portant. Special care needs to be taken to assure the compatability of the container /closure with the product and that the closure is capable of main-taining the integrity of the product.

F. Equipment

The qualification of equipment starts with the design or selection process, followed by installation and verification that the equipment functions as desired. Qualification of equipment also requires

the development of written procedures that describe the proper operation of the equipment, the devel-opment of a preventive maintenance program, the validation of cleaning procedures, and the training of personnel using or supervising the use of the equipment. Cleaning procedures must be shown to adequately remove product or dirt and to leave acceptably low levels of clean-ing agents, sol-vents, etc. If the equipment must be sterile or pyrogen-free, the procedures used to accomplish this have to be shown to be effective.

Computers are being used with greater frequency as process control equipment. Computers are commonly used to control sterilizers. Qualification of a computer is in most respects similar to the qualification of other process equipment. The computer-controlled system must be challenged to make sure that the system will function properly under a variety of conditions and with various inputs. Normally the equipment vendor will supply software programs to check out the system. The security of the system relative to inadvertent program modifications, power failures, etc., must be considered. Periodically the computer system must be checked to assure that it is still performing as expected.

G. Facilities

The qualification of a facility includes four phases:

design,
construction,
verification, and
ongoing maintenance and monitoring.

At the design or planning phase, the purpose of the facility, the product(s) to be manufac-tured, GMP and efficiency requirements, as well as cost, must be considered. The design of the critical systems (HVAC, water, etc.) is most important. Flow of material and personnel to avoid cross-overs and turn backs has to be studied. This leads to room and equipment layout. Room sur-faces, espe-cially in aseptic areas, have to be designed to be easily sanitized. Finally, everything needs to be documented-drawings, written specifications, etc.

The construction phase requires careful supervision to make sure that all the design specifica-tions are being met. The process of verifying that the constructed facility meets all the established requirements starts when construction commences and ends with the installation and qualification of the equipment and critical systems. The verification phase should be docu-mented and design specifications and engineering drawings modified if nec-essary. The last phase of qualifying a facility consists in establishing appropriate ongoing preventive maintenance, cleaning, sanitation, and environmental monitoring procedures.

H. Qualification of Manufacturing Stages

For each type of pharmaceutical dosage form there are various distinct stages in the manufactur-ing process that need to be qualified in order to validate the complete process. For a typical par-enteral product, such as a small volume parenteral, the stages are

Dispensing
Component preparation
Compounding
Sterile filtration
Filling
Terminal sterilization
Particulate inspection
Leak testing
Packaging

Additional stages would have to be qualified for aseptic bulk manufacture and filling, or for a lyophilized product.

I. Product Design

The product design consists of the formulation, container /closure system, basic manufacturing procedure, and quality control specifications and meth-odology. Chronologically, product design is the first component of validation to be studied. Although product design is normally the responsibility of the Research and Development function, it is wise to involve plant personnel, since their experience and knowledge of the plant's capabilities can be very valuable. A poorly designed product can make it impossible to validate and control a process. Consider the consequences of a formulation that is inherently unstable or inadequately preserved, specifications that are too tight, or analytical methodology that is not rugged.

IV. ORGANIZATION

The setting up of a validation program starts with the commitment of top management. Senior management support is necessary, since considerable resources will be necessary in order to carry out the program. It is the aim of this chapter to furnish the reader with material that can be used to show management the value of a validation program.

The composition of the validation team will depend on the component of the process being studied and the technical disciplines available (this will generally vary with the size of the company). Normally the following disciplines are involved in the plant validation program:

1. Quality Control
   - Chemical testing
   - Microbiology
   - Quality assurance
2. Production
3. Engineering
4. Product Development (Research and Development)

Other functions that frequently are involved are

Training-for qualification of personnel

Statistics-for experimental design and evaluation of data

Safety

Purchasing--qualification of vendors of raw and packaging materials

Drug Regulatory Affairs

Since process validation is a plant-wide operation, the program is ulti-mately the responsibility of the plant manager. The plant manager will usually appoint a validation coordinator to lead the validation team or in a small plant take on this task himself.

The role of Research and Product Development is important. For a new product R&D should provide the plant with the following:

A product design whose components--formulation, manufacturing procedure, analytical methodology, and material and product specifications--have been validated. The manufacturing procedure should be validated by R&D at least on a pilot-batch basis.

Identification of the critical variables in the product and process.

Tentative limits for these variables. The limits may have to be modified as a result of the process validation studies done by the plant, since many components of the process will be different than those used in R&D studies.

Methodology to measure, monitor, and control the critical variables.

The validation coordinator, with the help of a team, will set up the qual-ification program for each component of the process to be validated, make sure that the program is executed properly and on schedule, and coordinate the evaluation of the results obtained. The qualification program will con-sist of the following:

Flow diagram and description of the system

Qualification protocol, which includes:

- Parameters to be validated
- Methods to be used
- How results will be analyzed

Writing of standard operating procedures (SOPs) for the system, including in-process controls and monitoring procedures

Documentation of the qualification program

V. VALIDATION AND IN-PROCESS CONTROL

The purpose of validation is to identify the critical process parameters, es-tablish an acceptable range for these parameters, and provide a means of controlling them. Ongoing, daily, batch, in-process control and monitoring emanates from the validation study. Without in-process control, the vali-dation work becomes meaningless, an academic study. Consider, for example, a vali-dated autoclave being used without monitoring the temperature, or a still without monitoring con-ductivity. Furthermore, adequate in-process control frequently can eliminate the need for costly periodic revalidation of the process.

The role and importance of in-process control can be seen by examining its place in a total qual-ity assurance program. A total quality assurance program has four stages:

Development: This is the product design phase and also includes the initial validation stud-ies.

In-process control /monitoring**:** Consists of the ongoing, daily control and monitoring of the process.

Auditing: A periodic process audit verifies that procedures estab-lished during validation are being complied with and that these pro-cedures are still adequate. "Putting a program in writing does not ensure that it will be followed, nor does it, in and of itself, provide the feedback necessary to correct and update programs and proc-esses" [6].

Modification*:* There are a variety of reasons for changing a system productivity improve-ment, lower costs, revised quality requirements, new equipment, new processes, etc. Sometimes we find that a proc-ess can change imperceptibly with small modifications, so that the resulting system is considerably different than the original. Changes in the proc-ess require that it be *revalidated.*

In-process control is too important to be left to chance or to be handled in an arbitrary manner. Control charts are a very useful, statistically based tool for in-process control. In its simplest form, the control chart consists of a plot of the variable being monitored vs. time, with action levels es-tab-lished at plus or minus 2 and/or 3 standard deviations. This technique pro-vides the operator with the means of determining whether the process is under control and whether the product re-sulting from the process is likely to meet specifications. For a parenteral operation a control chart is useful for control of filling, for analysis of environmental control data, for accumula-tion and analysis of assay data, microbial counts of water, etc.

VI. VALUE OF VALIDATION

As indicated earlier, the main advantages to be obtained from validating a process are cost reduction, process optimization, and assurance of quality, with compliance with regulatory requirements as an added bonus. This is not to imply that compliance with regulations is unimportant; however, more is to be gained and perhaps a better job done by looking at the more positive aspects of validation, i.e., those aspects that affect the bottom line of an operation. In this section some of the potential returns that can be expected from a company's investment in validation will be reviewed.

A. Reduction of Quality Costs

Traditionally, quality costs are divided into prevention, appraisal, internal failure, and external failure costs. These costs are defined in Table 1.

There is little published data on total quality costs [7]. The author is not aware of any data published for the pharmaceutical or parenteral industry. However, that is not to say that **the** pharmaceutical industry has not studied quality costs, and some information is available at least on an informal basis. A conservative estimate is that quality costs for the pharmaceutical industry in general are about 10-15$ of the total manufacturing costs. The quality costs for the parenteral industry are undoubtedly higher, because parenteral products generally involve more sophisticated technology and special re-quirements (sterility, for example) due to the nature of their use involve higher prevention and appraisal costs. Also, failure costs in the parenteral industry are generally higher due to the high costs of materials and processing.

While these measurable costs are high, the hidden costs can be greater. Consider the cost of recalls, complaints, and law suits. A recall can ruin a product or company at worst and at best tarnish the product and the

TABLE 1 Quality Costs

Preventive costs are costs incurred in order to prevent failures and/or reduce the appraisal costs.

- Quality planning
- Vendor approval system
- Training
- Documentation --SOPs, monographs
- Preventative maintenance
- Calibration
- Sanitation
- Process validation
- Quality assurance auditing and self-inspections
- Annual review of data or trend analysis

Appraisal costs are costs of inspection, testing, and quality evaluation. Some examples of appraisal costs are

a. Inspection /testing of raw and packaging materials
b. Inspection /testing of in-process materials
c. Inspection /testing of finished products

Stability testing

Internal failure costs are costs associated with nonconforming material--material that does not meet quality standards-still in the company's possession. Some examples of internal failure costs are

- Rejects
- Reworks

Reinspections
Retests
Wastage/scrap
Troubleshooting
Sorting substandard material

External failure costs are costs associated with a nonconformance con-dition after the product has left the company's ownership. Some examples of external failure costs are

Recalls
Complaints
Returns due to quality-related problems

Company’s reputation, resulting in decreased sales and profit. Persistent failure problems in a plant can adversely affect morale and create friction between departments, and between man-agement and the workers.

It is obvious that a validated and controlled process, as defined in this chapter, will result in fewer internal failures-fewer rejects, reworks, re-tests, reinspections, and wastage. Validation makes it possible to do the job right the first time. Also, a scientifically studied and controlled process makes it unlikely that defective products will be shipped to the consumer--thus, no recalls or com-plaints.

Spending resources on prevention (validation) will also enable the phar-maceutical manufacturer to decrease appraisal (testing and inspection) costs. Theoretically, for a validated process for which we have absolute control of all variables, there should be no need to perform any inspec-tions or testing on the finished product. As this ideal is approached, Quality Control de-partment testing can be decreased correspondingly. Some examples include

Sterility testing of terminally sterilized products given a validated/ controlled autoclave

Inspection for particulates given control of the sources of particulate contamination

Components testing from suppliers with validated /controlled processes

In those cases where testing cannot be completely eliminated, validation should allow us to re-duce the frequency of testing or reduce the number of samples tested.

Training is one of the components of validation and prevention cost.

"The goal of every manufacturer is to produce a quality product in a rea-sonable amount of time at a minimum cost. The cost of training is minimal when one compares it to the loss of revenue that may occur as a result of inadequate training. Remember the adage: 'If you think education is expensive, try ignorance.'

Properly trained employees help reduce errors in the manufacturing process. Training helps to reduce the time a company spends correcting errors in documentation and the money it spends reworking a product. A company minimizes the possibility of costly recalls by developing a good method of manufacturing and by training its employees to perform according to that method. Training helps to place the responsibility of protecting the company's revenues in the employees hands" [8].

B. Process Optimization

When a process is thoroughly studied, some way of optimizing it is inevitably found. The optimi-zation of a process for maximum efficiency while maintain-ing quality standards is a consequence of validation. The dictionary defines "to optimize" as "to make as effective, perfect or useful as possible"; we would add "at the lowest cost." The optimization of the facility, equipment, sys-tems, closures, etc., results in a product that meets quality requirements at the lowest cost. Trained, qualified people are a key element in any proc-ess and thus have the greatest impact on improving efficiency and produc-tivity. In this context G69P training cannot be separated from a total train-ing program that includes how to do the job correctly, easily, and rapidly.

Some areas where experience shows that optimization is possible as a result of validation studies are the following:

- ⇒ Optimum batch sizes relative to availability of equipment and person-nel and size of fa-cility.
- ⇒ Decreased downtime of equipment due to programmed preventative maintenance based on thorough understanding of equipment and process.
- ⇒ Reduced sterilization times due to studies of bioburden, validation and control of auto-clave, etc.
- ⇒ Reduced mixing times.
- ⇒ Reduced overfill of liquids due to knowing limits /capabilities of filling equipment.
- ⇒ Faster and more accurate analytical test procedures.
- ⇒ Development of standards for the process-standards for labor, equipment, yields, etc.-- that results in better production control and resource allocation.
- ⇒ Better product or component specifications due to challenging the specifications. Are they reasonable and appropriate in light of the use of the product?
- ⇒ Reduced energy costs. Properly calibrated temperature gauges, for example, can pre-vent the overheating of a Water-for-Injection storage vessel, sterilizer, etc., which would result in a wastage of energy.

An example of the optimization resulting from instrument calibration given by Bremmer:

"We have had two clearly documented cases where Calibration information identified poor instru-ment performance in a fermentation process. In one case, subsequent instrument replacement led to improved yields, attri-butable to improved instrument accuracy. In the other case, improved yields and improved ferment or turnaround times were realized. At this point it should be noted that it is not always the Calibration Program itself that improves instrument performance, yields or quality. The Calibration, however, often provides hints which allow qualified people to find solu-tions" .

C. Assurance of Quality

"Validation is an extension of the concepts of quality assurance since close control of the process is necessary to assure product quality and it is not possible to control a process properly without thorough knowledge of the capabilities of that process" [10].

In other words, validation and process control are at the heart of GMPs. Without validated and controlled processes it is impossible to pro-duce quality products consistently.

In the past, control of quality consisted largely of end-product testing and inspection. End-product testing and inspection have inherent deficien-cies relative to assurance of quality. Process valida-tion and in-process control are far superior methods of quality assurance.

The limitations of product testing and the value of validation for assur-ing quality of a batch is offi-cially recognized by the U. S. Pharmacopeia (USP):

"However, it is not to be inferred that application of every analytical procedure in the monograph to samples from every production batch is necessarily a prerequisite for assuring compliance with

Pharmacopeial standards before the batch is released for distribution. Data derived from manufacturing *process validation* studies and from *in-process controls* sometimes may provide greater assurance that a batch meets a particular monograph requirement than analytical data derived from an examination of finished units drawn from that batch" [11].

Inspection procedures fall into two categories: 100% inspection or in-spection of a statistical sample. Obviously, inspecting a statistical sample does not give absolute assurance that each unit produced will meet speci-fications. For a given level of defects and a given sampling plan, the probability of a defective item not being discovered can be calculated. Even 100% inspection may not be better: "Yet research shows that, even in 100% inspection, up to 150 of defective items are not detected" [12].

An example of the fact that *one can't inspect quality into a product is* that 100$ inspection of parenterals for visible particulates has not resulted in particulate-free products on the market. The quality of parenterals, from the point of view of absence of visible particulates, is better today than 10 years ago, because the pharmaceutical industry has located the sources of particulates, improved the process, and has better process control.

Similarly, end-product testing, in the absence of validation, gives little assurance of quality for a number of reasons, among which are

- ⇒ Very limited sample size.
- ⇒ The limited number of tests performed on a sample. For example, it is impractical to test for all possible impurities or contaminants.
- ⇒ The limited sensitivity of the test.

Although these limitations apply to all product testing, they are most dramatically illustrated with respect to sterility testing.

"The production of sterile products is probably the best example to illus-trate the importance of proper manufacturing conditions and practices (Process Validation, GMPs) over end testing. Consider the use of an end product sterility test, for instance, to demonstrate sterility assurance of a production lot. This particular end product testing approach is flawed in several ways. First of a11, the nature of the test is such that a finding of no growth in a limited test *sample* cannot be extrapolated with much certainty to characterize the nature of the entire lot. This is because the contamination which the test is intended to detect, is not necessarily distributed uniformly throughout the entire lot. A more significant flaw, however, is the inherent insensitivity of sterility tests. For example, the sampling requirements of the USP Sterility Test are such that it can only detect (with a 90% confidence level) a lot in which 10°s of the units are contaminated. 10% is a rather high level of contam-ination; and at only a 90% confidence level, that means that for one out of every 10 tests, you may not be able to detect even this level of con-tamination" [13].

Again the USP recognizes the limitations of the sterility test and the importance of process controls:

"It is recognized that sterility tests may not detect microbial contamination of a low order of magnitude in a lot of product. . . . The statistical limitations of the sampling requirements . . . are clear . . .. Negative results from a valid sterility test are indicative of the sterility of the lot only if the records of all pertinent sterilization and microbiological de-contamination procedures and aseptic processing stages subsequent to sterilization indicate that these processes have been carried out in com-plete accordance with the written standard operating procedures in the manufacturer's files, and that these are in compliance with current com-pendial and regulatory requirements and principles for the production of Pharmacopeial products" [14].

It can be concluded that assurance of product sterility should rely more on manufacturing controls, especially a validated and controlled steam ster-ilizer, than on sterility testing.

D. Safety

Validation can also result in increased operator safety. For example, gauges used on equipment that is designed to operate at certain temperatures and pressures must be reliable, i.e., they must be calibrated.

VII. LIMITATIONS

There are no inherent limitations in the concept of validation relative to its ability to assure quality and reduce costs, but on the practical side, valida-tion is not an absolute cure-all. Some of the practical limitations are people, availability of facilities and equipment, cost, inadequate technol-ogy, etc.

People, while being a company's greatest asset, are also the cause of many problems with a process. A validated process, in order to function properly, requires that people follow proce-dures, do their job conscientious-ly and without error, do not modify the system, etc. People defi-ciencies that affect product quality and productivity are not confined to operators; gen-erally, the deficiencies of supervisors and management are more significant. An operator can do little if management does not provide adequate tools to do the job and control the process--adequate equipment, facilities, systems, and procedures.

This leads to the consideration of costs-costs of process validation. Management must allocate resources to a validation program, and since re-sources are always limited, this necessarily leads to some compromises in the validation program. One can always spend more money on facilities, equip-ment, system development, in-process controls, and validation studies. A 100% assurance of quality is impossible. A definition of validation that illu-strates this is "the documentation and evaluation of evidence to provide a *high degree of assurance* that the process with proper con-trols delivers a product of predetermined quality" [15].

A high degree of assurance is all that can practically be expected from validation. The degree of assurance to be attained is a balancing act between cost and benefit. The quality standard must be examined relative to the use of the product and what the consumer expects and requires of the product. Specifications need to be challenged in this light, as the manufacturing proc-ess is challenged. From the consumer's point of view, too much quality assurance (at a higher cost) may be as undesirable as too little. Does the consumer obtain any real benefit from a sterility confidence level of 109 vs 10^6, or in other words, "Does it make sense to employ aseptic filling opera-tions for a terminally sterilized product?" [16]. Absolute assurance of sterility is unattain-able; a high level of confidence is possible. Complete assurance of the absence of all impurities is not feasible.

Validation can provide a high assurance of quality and can assist in reducing manufacturing costs, but there will still be some risk to product quality, and medicines will still cost money.

VIII. SUMMARY

Process validation is a concept that is fundamental to GMPs and any Quality Assurance program. There is no effective Quality Assurance program with-out validation.

Validation studies inevitably lead to process optimization, better produc-tivity, and lower manufac-turing costs. The investment made in validation, like the investment made in qualified people, can only provide an excellent return.

Part 2:

TOTAL APPROACH TO PHARMACEUTICAL PROCESS VALIDATION

It has been said that there is no specific basis for requiring a separate set of process validation guidelines since the essentials of process validation are embodied within the purpose and scope of the present cGMP regulations [2]. With this in mind, the entire cGMP document, from subpart B through subpart M, may be viewed as being a set of principles applicable to the overall process of manufacturing, i.e., medical devices as well as drug products, and thus may be subjected, subpart by subpart, to the application of the principles of qualification, validation, control. in addition to requalification and revalidation, where applicable. Although not a specific requirement of current regulations, such a comprehensive validation approach with respect to each subpart of the cGMP document has been adopted by many drug firms.

WHY ENFORCE PROCESS VALIDATION?

Process validation should result in fewer product recalls and troubleshooting assignments in manufacturing operations. In the first edition of Pharmaceutical Process Validation we suggested that the number of recalls reported by the FDA could be used to assess the effectiveness of industry-wide validation programs.

Process validation should result in more technically and economically sound products and their manufacturing processes. In the old days R & D "gurus" would literally hand down the "go" sometimes overformulated product and accompanying obtuse manufacturing procedure, usually with little or no justification or rationale provided. Today, under the recently installed FDA preapproval inspection program [30], such actions are no longer acceptable. The watchword now is to provide scientifically sound justifications (including qualification and validation documentation) for everything coming out of the pharmaceutical R & D function.

WHAT IS PROCESS VALIDATION?

Unfortunately, there is still much confusion as to what process validation is and what constitutes process validation documentation. At the beginning of this introductory chapter several different definitions for process validation were provided, which were taken from FDA guidelines and CGMPs. Chapman calls process validation simply "organize, documented common sense" [33].

One problem is that we use the term validation generically to cover the entire spectrum of CGMP concerns, most of which are essentially facility, equipment,procedures, and process qualification. The specific term process validation should be reserved for the final stages of the product and process development sequence. The essential or key steps or stages of a successfully completed product and process development program are presented in Table 3 [34].

The end of the sequence that has been assigned to process validation is derived from the fact that the specific exercise of process validation should never be designed to fail, Failure in carrying out the process validation assignment is often the result of incomplete or faulty understanding of the process's capability, in other word, what the process and cannot do under a given set of operational cir-

cumstances. In a well-designed, well-run overall validation program, most of the budget dollars should be spent on facilities, equipment, components, methods, and process qualification. In such a program, the formalized final process validation sequence provides only the necessary process validation documentation required by the FDA, in other words, the "Good Housekeeping Seal of Approval," which shows that the manufacturing process in under a state of control.

WHAT ARE THE PROCESS VALIDATION OPTIONS?

The guidelines on general principles of process validation [1] mention three options. They are prospective process validation(also called premarket validation), retrospective process validation and revalidation. In actuality there ar e four possible options.

A. Prospective Process Validation

In prospective process validation, an experimental plan called the validation protocol is executed (following completion of the qualification trials) before the process is put into commercial use. Most validation efforts require some degree of prospective experimentation to generate validation support data. This particular type of process validation is normally carried out in connection with the introduction of new drug products and their manufacturing processes. The formalized process validation program should never be undertaken unless and until the following operations and procedures have been completed satisfactorily;

1. The facilities and equipment in which the process validation is to be conducted meet CGMP requirements (completion of installation qualification)
2. The operators and supervision personnel,, who will be "running" the validation batch(es), have an understanding of the process and tits requirements
3. The design, selection, and optimization of the formula have been completed
4. The qualification trials using (10 x size) pilot-laboratory batches have been completed, in which the criticalprocessing steps and process variables have been identified, and the provisional control limits for each critical test parameter have been provided
5. Detailed technical information on the product and the manufacturing process have been provided, including documented evidence of product stability
6. Finally,at least one qualification trial of a pilot-production (100 x size) batch has been made and shows, upon scale-up, that there were no significant deviations from the expected performance of the process

The steps and sequence of events required to carry out a process validation assignment are outlined in Table 10. The first half of the procedure is similar to that developed for process capability design and testing. The objective of prospective validation is to prove or demonstrate that the process will work in accordance with validation protocol prepared for the pilot-production (100 x size) trials.

The stately selected for process validation should be simple and straight-forward. The following five points are presented here for the reader's consideration:

1. The use of different lots of raw materials should be included, i.e., active drug substance and major excipients.
2. Batches should be run in succession and on different days and shifts (the latter condition, if appropriate).
3. Batches should be manufactured in the equipment and facilities designated for eventual commercial production.
4. Critical process variables should be set within their operating ranges and should not exceed their upper and lower control limits during process operation. Output responses should be well within finished product specifications.

5. Failure to meet the requirements of the validation protocol with respect to process input control should be subjected to process requalification and subsequent revalidation following a thorough analysis of process data and formal discussion by the validation team.

B. Retrospective Validation

The retrospective validation option is chosen for established products whose manufacturing processes are considered stable(e.g., long-history state-of-control operation) and when, on the basis of economic considerations alone and resource limitations, prospective qualification and validation experimentation cannot be justified. Prior to undertaking retrospective validation, wherein the numerical inprocess and/or end-product test data of historic production batches are subjected to statistical analysis, the equipment, facilities, and subsystems used in connection with the manufacturing process must be qualified and validated in conformance with CGMP requirements.

Using either data-based computer systems [54,55] or manual methods, retrospective validation may be conducted on the following manner:

1. Gather the numerical values from the completed batch record and include assay values, end-product test result, and in-process data.
2. Organize these data in a chronological sequence, according to batch manufacturing data using a spreadsheet format.
3. Include data from at least the last 20-30 manufactured batches for analysis. If the number of manufactured batches is less than 20, then include all manufactured batches in your analysis.
4. Trim the data by eliminating test results from noncritical processing steps and delete all gratuitous numerical information.
5. Subject the resultant data to statistical analysis and evaluation.
6. Draw conclusions as the state of control of the manufacturing process based upon the analysis of retrospective validation data.
7. Issue a report of your findings (documented evidence).

One or more of the following output values (measured response),

which have been shown to be critical in terms of the specific manufacturing process being evaluated, are usually selected for statistical analysis.

Solid Dosage Forms

1. Individual assay results from content uniformity resting
2. Individual tablet hardness values
3. Individual tablet thickness value
4. Tablet or capsule weight variation
5. Individual tablet or capsule dissolution tine (usually at $t_{50\%}$) or disintegration time
6. Individual tablet or capsule moisture content

Semisolid and Liquid Dosage Forms

1. pH value (aqueous system)
2. Viscosity
3. Density
4. Color or clarity values
5. Average particle size or distribution

6. Unit weight variation and/or potency values

The statistical methods that may be employed to analyze numerical output data from the manufacturing process are listed as follows:

1. Basic statistics (mean, standard deviation, and tolerance limits) [56]
2. Analysis of variance (ANOVA and related techniques) [56]
3. Regression analysis [56]
4. Cumulative sum analysis (CUSUM) [57]
5. Cumulative difference analysis [57]
6. Contort charting (averages and range) [58,59]\

Control charting,with the exception of basic statistical analysis, is probably the most useful statistical technique one might use to analyze retrospective and concurrent process data. Control charting forms the bases of modern statistical process control.

C. Concurrent Validation

In-process monitoring of critical processing steps and end-product testing of current production can provide documented evidence to show that the manufacturing process in a state of control. Such validation documentation can be provided from the test parameter and data sources disclosed in the section on retrospective validation.

Test parameter	Data source
Average unit potency	End-product testing
Content uniformity	End-product testing
Dissolution time	End-product testing
Weight variation	End-product testing
Powder-blend uniformity	In-product testing
Moisture content	In-product testing
Particle or granule size distribution	In-product testing
Weight variation	In-product testing
Tablet hardness	In-product testing
pH value	In-product testing
Color or clarity	In-product testing
Viscosity or density	In-product testing

Not all of the in-process tests enumerated above are required to demonstrate that the process is in a state of control. Selections of test parameters should be made on the basis of the critical processing variable s to be evaluated.

D. Revalidation

Conditions requiring revalidation study and documentation are listed as follows:

1. Change in a critical component (usually refers to raw materials)

2. Change or replacement in a critical piece of modular (capital) equipment
3. Change in a facility and/or plant (usually location or site)
4. Significant (usually order of magnitude) increase of decrease in batch size
5. Sequential batches that fail to meet product and process specifications

In some situations performance requalification studies may be required prior to undertaking specific revalidation assignments.

Approved packaging is normally selected after completing package performance qualification testing as well as product compatibility and stability studies. Since in most cases (exceptions: transdermal delivery systems, diagnostic tests, and medical devices) packaging is not intimately involved in the manufacturing process of the product itself, it differs from other factors, including raw materials, equipment,and formulation and facility changes ,all of which may profoundly influence product quality and performance. Package changes should be handled in existing, separate product stability testing programs.

Revalidation remains an important validation option and should be considered whenever the continued state of control and reliable performance of the manufacturing process are in doubt.

Part 3:

Process Validation Guidance

Contents

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Introduction

Process validation is a term used in the medical device industry to indicate that a process has been subject to such scrutiny that the result of the process (a product, a service or other outcome) can be practically guaranteed. This is vitally important if the predetermined requirements of the product can only be assured by destructive testing.

Processing deficiencies may only become apparent after an intermediate component is further processed or the finished product is in use. Validation of a process entails demonstrating that, when a process is operated within specified limits, it will consistently produce product complying with predetermined (design) requirements.

The medical device industry encompasses a wide range of technologies and applications, ranging from simple hand tools to complex computer-controlled surgical machines, from implantable screws to artificial organs, from blood-glucose test strips to diagnostic imaging systems and laboratory test equipment. These devices are manufactured by companies of varied size, structure, volume of production, manufacturing processes and management methods. These factors, especially production volume and number of manufacturing steps per unit (e.g. soldering or welding steps) significantly influence how process validation is actually applied. Given this diversity, this guidance does not suggest particular methods of implementation, and therefore, must not be used to assess compliance with quality system requirements. Rather the intent is to expand on quality system requirements with practical explanations and examples of process validation principles. Manufacturers can and should seek out/select technology-specific guidance on applying process validation to their particular situation.

This guidance provides general suggestions on ways manufacturers may prepare for and carry out process validations. Other ways may be equally acceptable; some regulatory requirements place the responsibility on the manufacturer to specify those processes which require validation and the qualification of personnel who operate validated processes. Regardless of the method used to validate the process, records of all validations activities should be kept and the final outcome documented.

While the completion of process validation is a regulatory requirement, a manufacturer may decide to validate a process to improve overall quality, eliminate scrap, reduce costs, improve customer satisfaction, or other reasons. Coupled with properly controlled design activities; a validated process may well result in a reduced time to market for new products.

In general, the validation of a process is the mechanism or system used by the manufacturer to plan, obtain data, record data, and interpret data. These activities may be considered to fall into three phases: 1) an initial qualification of the equipment used and provision of necessary services – also know as installation qualification (IQ); 2) a demonstration that the process will produce acceptable results and establishment of limits (worst case) of the process parameters – also known as operational qualification (OQ); and 3) and establishment of long term process stability – also known as performance qualification (PQ).

Many processes are controlled by computers. While the computer software may be considered an integral part of the process, this guideline does not cover software validation.

While the theory of process validation is reasonably straightforward, the decision of the manufacturer to evaluate every process for potential validation may lead to uncertainty. Some regulatory requirements state that every process that cannot be fully verified by subsequent inspection or test be validated. Deviation from this principle may be allowed by local regulation, but should be fully justified by the manufacturer on the basis of lack of risk to patient. Guidance is provided for reaching decisions on whether to validate or not.

1 Purpose and scope

1.1 Purpose This process validation guidance is intended to assist manufacturers in understanding quality system requirements concerning process validation.

1.2 Scope This document has general applicability to manufacturing (including servicing and installation) processes for medical devices. Specific recommendations for verification of design output and design validation is included in the GHTF document covering design control.

2 Definitions

For this document, the following definitions apply. Terms other than those defined herein may be found in the literature.

2.1 Installation qualification (IQ): establishing by objective evidence that all key aspects of the process equipment and ancillary system installation adhere to the manufacturer's approved specification and that the recommendations of the supplier of the equipment are suitably considered.

2.2 Operational qualification (OQ): establishing by objective evidence process control limits and action levels which result in product that meets all predetermined requirements.

2.3 Performance qualification (PQ): establishing by objective evidence that the process, under anticipated conditions, consistently produces a product which meets all predetermined requirements.

2.4 Process validation: establishing by objective evidence that a process consistently produces a result or product meeting its predetermined requirements.

2.5 Process validation protocol: a document stating how validation will be conducted, including test parameters, product characteristics, manufacturing equipment, and decision points on what constitutes acceptable test results.

2.6 Verification: confirmation by examination and provision of objective evidence that the specified requirements have been fulfilled.

3 Processes that should be validated

3.1 Special processes

Special processes (those processes for which the product cannot be fully verified) need special consideration. In the medical device industry these considerations often lead to process validation. National or regional regulations may require that process validation be performed for special processes.

3.2 Process validation within the quality system

Process validation is part of the integrated requirements of a quality system. It is conducted in the context of a system including design control, quality assurance, process control, and corrective and preventive action.

The interrelationship of design control and process development may, for some technologies, be very closely related. For others the relationship may be remote. The product should be designed robustly enough to withstand variations in the manufacturing process and the manufacturing process should be capable and stable to assure continued safe products that perform adequately. Often this results in a very interactive product development and process development activity.

Daily quality assurance activities are conducted as specified by the process control plan which is often largely developed during process validation.

Corrective actions often identify inadequate processes/process validations. Each corrective action applied to a manufacturing process should include the consideration for conducting process validation/revalidation.

3.3 Process validation decision

The following model may be useful in determining whether or not a process should be validated:

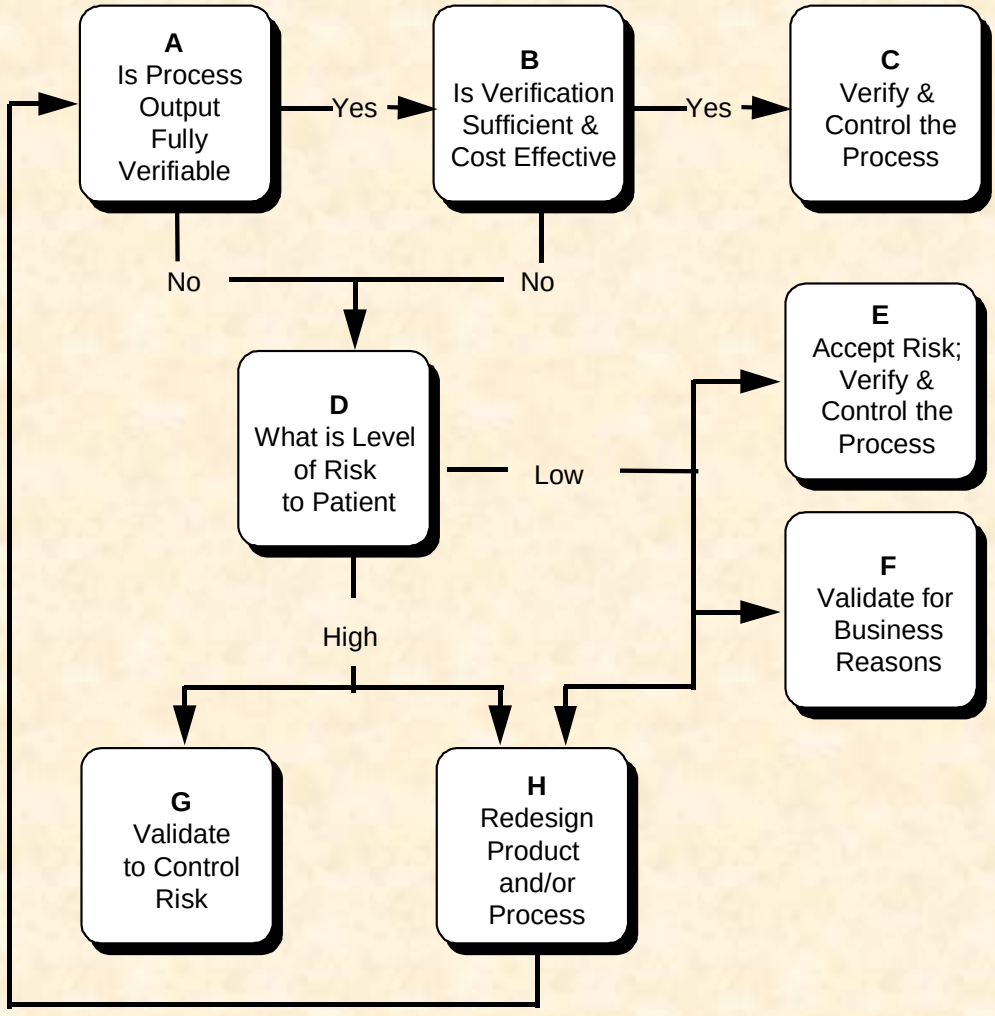

Figure 1: Process validation decision tree

The model shown describes a decision tree that a manufacturer can follow when deciding on whether a process needs to be validated. The process under consideration in this model is the simplest possible - many processes may be large and/or a complex set of sub-processes.

Each process should have a specification describing both the process parameters and the output desired. The manufacturer should consider whether the output can be fully verified by inspection and/or test (A). If the answer is positive, then the consideration should be made as to whether or not verification alone is sufficient to eliminate unacceptable risk and is a cost effective solution (B). If yes, the output should be verified and the process should be appropriately controlled (C).

If the output of the process is not verifiable then the manufacturer should consider the risk to the patient of the process or the final product (D). If the risk is high then the decision should be to validate the process (G); alternatively, it may become apparent that the product or process should be redesigned to reduce variation and improve the product or process (H).

If the risk is low, then the manufacturer may consider justifying not validating the process and accept those risks (E). Also, if the risk is low, management may decide to validate a process even though the output of the process is verifiable (F). This may be because the cost of ensuring compliance with output requirements of a non-validated process is too high, or because the manufacturer may not be prepared to accept the risk-to-patient of verification only, or for other reasons. The risk or cost may also be reduced by redesigning the product or process to a point where simple verification is an acceptable decision (H).

3.4 Examples

The following table is a list of examples of processes which normally: (1) should be validated, (2) may be satisfactorily covered by verification, and (3) processes for which the above model may be useful in determining the need for validation.

(1) Processes which should be validated

Sterilization processes
Clean room ambient conditions
Aseptic filling processes
Sterile packaging sealing processes
Lyophilization process
Heat treating processes
Plating processes
Plastic injection molding processes

(2) Processes which may be satisfactorily covered by verification

Manual cutting processes
Testing for color, turbidity, total pH for solutions
Visual inspection of printed circuit boards
Manufacturing and testing of wiring harnesses

(3) Processes for which the above model may be useful in determining the need for validation

Cleaning processes
Certain human assembly processes
Numerical control cutting processes
Filling processes

To determine the level of risk to the patient in the context of this guidance, it is suggested that the failure modes of the device be analyzed relative to the manufacturing process. If a failure of the process could cause a failure of the device, that process failure should be evaluated for its severity and frequency and subsequent failure rate of the device. Guidance on risk management can be found in other standards and guidances.

The output of a process may be fully verifiable and the overall process may not require validation. However, software used to automate such processes should be validated for its intended use.

Manufacturers should document the rationale used for not validating processes, including risk analysis and the reasons as to why verification and/or process control are sufficient.

4 Statistical methods and tools for process validation

There are many methods and tools that can be used in process validation. A primer on statistics and process validation is provided in Annex A as a guide through the basic concepts. Control charts, capability studies, designed experiments, tolerance analysis, robust design methods, failure modes and effects analysis, sampling

plans, and mistake proofing are some of the examples.

5 Conduct of a validation

5.1 Getting started

A consideration should be given to form a multi-functional team to plan and oversee the validation activities. A team approach will help assure the validation processes are well thought out, the protocols are comprehensive and that the final packages are well documented and easy to follow. The team should advise “what could go wrong”. The team also provides an opportunity for key functional areas to communicate early about important new and changed products and processes and can foster cooperation.

Members of the validation team could include representatives from or personnel with expertise in:

- Quality Assurance
- Engineering
- Manufacturing

Others depending on company organization and product types:

- Laboratory
- Technical Services
- Research & Development
- Regulatory Affairs
- Clinical Engineering
- Purchasing/Planning

Once the validation team has been formed, the next step is to plan the approach and define the requirements. Many manufacturers develop what is referred to as a master validation plan which identifies those processes to be validated, the schedule for validations, interrelationships between processes requiring validation and timing for revalidations. Once these have been established,

and the purpose and scope for validations are clearly stated and known, protocol development can commence.

Following is a list of activities which may be used as a checklist to review validation activity:

- Form multi-functional team for validation
- Plan the approach and define the requirements
- Identify and describe the processes
- Specify process parameters and desired output
- Decide on verification and/or validation
- Create a master validation plan
- Select methods and tools for validation
- Create validation protocols
- Perform IQ, OQ, PQ and document results
- Determine continuous process controls
- Control the process continuously

5.2 Protocol development

Detailed protocols for performing validations are essential to ensure that the process is adequately validated. Process validation protocols should include the following elements:

- Identification of the process to be validated
- Identification of device(s) to be manufactured using this process
- Objective and measurable criteria for a successful validation
- Length and duration of the validation
- Shifts, operators, equipment to be used in the process
- Identification of utilities for the process equipment and quality of the utilities
- Identification of operators and required operator qualification
- Complete description of the process
- Relevant specifications that relate to the product, components, manufacturing materials, etc.
- Any special controls or conditions to be placed on preceding processes during the validation
- Process parameters to be monitored, and methods for controlling and monitoring
- Product characteristics to be monitored and method for monitoring
- Any subjective criteria used to evaluate the product
- Definition of what constitutes non-conformance for both measurable and subjective criteria
- Statistical methods for data collection and analysis
- Consideration of maintenance and repairs of manufacturing equipment
- Criteria for revalidation

For all three phases, IQ, OQ, and PQ, based on product/process requirements:

- Determine what to verify/measure
- Determine how to verify/measure
- Determine how many to verify/measure, i.e. statistical significance
- Determine when to verify/measure
- Define acceptance/rejection criteria

Define required documentation

Knowing exactly what the product requirements are and what key parameters will be necessary to answer the questions of what to measure. Seal thickness, seal strength, pressure testing and visual defects of samples are examples of measurable parameters.

Utilizing statistically valid techniques such as sampling, design experiments, Taguchi methods, response surface studies and component swapping are statistically valid techniques to answer the questions of how many to measure. Utilization of standard test methods such as such as those contained in international or national standards will provide guidance in how to measure specific parameters. Also, it is important to ensure test methods replicate actual use conditions.

During the conduct of various phases of validation, the protocol should address the resolution of discrepancies. Some deviations in established protocol may not negate the results. Each deviation should be addressed, evaluated and a conclusion drawn as to acceptance or rejection of the results. As a result, process control procedures may require modification and those modifications should be validated as part of the overall process.

Addressing all product and process requirements and the establishment of specific criteria for each requirement, upper and lower limits based on product specifications and established standards will help define the acceptance/rejection criteria.

5.3 Installation qualification (IQ)

Simply put, IQ means is it installed correctly? Important IQ considerations are:

Equipment design features (i.e. materials of construction cleanability, etc.)

Installation conditions (wiring, utilities, functionality, etc.)

Calibration, preventative maintenance, cleaning schedules

Safety features

Supplier documentation, prints, drawings and manuals

Software documentation

Spare parts list

Environmental conditions (such as clean room requirements, temperature, humidity)

Sometimes activities are conducted at the equipment supplier's site location prior to equipment shipment. Equipment suppliers may perform test runs at their facilities and analyze the results to determine that the equipment is ready to be delivered. Copies of the suppliers' qualification studies should be used as guides, to obtain basic data, and to supplement installation qualification. However, it is usually insufficient to rely solely upon the validation results of the equipment supplier. Each medical device manufacturer is ultimately responsible for evaluating, challenging, and testing the equipment and deciding whether the equipment is suitable for use in the manufacture of a specific device(s). The evaluations may result in changes to the equipment or process.

5.4 Operational qualification - (OQ)

In this phase the process parameters should be challenged to assure that they will result in a product that meets all defined requirements under all anticipated conditions of manufacturing, i.e., worst case testing. During routine production and process control, it is desirable to measure process parameters and/or product characteristics to allow for the adjustment of the manufacturing process at various action level(s) and maintain a state of control. These action levels should be evaluated, established and documented during process validation to determine the robustness of the process and ability to avoid approaching "worst case conditions."

OQ considerations include:

- Process control limits (time, temperature, pressure, linespeed, setup conditions, etc.)
- Software parameters
- Raw material specifications
- Process operating procedures
- Material handling requirements
- Process change control
- Training
- Short term stability and capability of the process, (latitude studies or control charts)
- Potential failure modes, action levels and worst-case conditions (Failure Mode and Effects Analysis, Fault Tree Analysis)

The use of statistically valid techniques such as screening experiments to establish key process parameters and statistically designed experiments to optimize the process can be used during this phase.

5.5 Performance qualification - (PQ)

In this phase the key objective is to demonstrate the process will consistently produce acceptable product under normal operating conditions. Please note the guidance for process stability in Annexes A and B “Methods and tools for process validation”.

PQ considerations include:

- Actual product and process parameters and procedures established in OQ
- Acceptability of the product
- Assurance of process capability as established in OQ
- Process repeatability, long term process stability

Challenges to the process should simulate conditions that will be encountered during actual manufacturing. Challenges should include the range of conditions as defined by the various action levels allowed in written standard operating procedures as established in the OQ phase. The challenges should be repeated enough times to assure that the results are meaningful and consistent.

Process and product data should be analyzed to determine what the normal range of variation is for the process output. Knowing the normal variation of the output is crucial in determining whether a process is operating in a state of control and is capable of consistently producing the specified output.

One of the outputs of OQ and PQ is the development of attributes for continuous monitoring and maintenance. Process and product data should also be analyzed to identify any variation due to controllable causes. Depending on the nature of the process and its sensitivity, controllable causes of variation may include:

- Temperature
- Humidity
- Variations in electrical supply
- Vibration
- Environmental contaminants
- Purity of process water
- Light

Human factors (training, ergonomic factors, stress, etc.)

Variability of materials

Wear and tear of equipment

Appropriate measures should be taken to eliminate controllable causes of variation. Eliminating controllable causes of variation will reduce variation in the process output and result in a higher degree of assurance that the output will consistently meet specifications.

Final report

At the conclusion of validation activities, a final report should be prepared. This report should summarize and reference all protocols and results. It should derive conclusions regarding the validation status of the process. The final report should be reviewed and approved by the validation team and appropriate management.

6 Maintaining a state of validation

6.1 Monitor and control

Trends in the process should be monitored to ensure the process remains within the established parameters. When monitoring data on quality characteristics demonstrates a negative trend, the cause should be investigated, corrective action may be taken and revalidation considered.

6.2 Changes in processes and/or product

Any changes in the process and /or product including changes in procedures, equipment, personnel, etc. should be evaluated to determine the affects of those changes and the extent of revalidation considered.

6.3 Continued state of control

Various changes may occur in raw materials and/or processes, which are undetected, or considered at the time to be inconsequencial. (An example of this type of process is sterilization.) These changes may cumulatively affect the validation status of the process. Periodic revalidation should be considered for these types of processes.

6.4 Examples of reasons for revalidation

Revalidation may be necessary under such conditions as:

change(s) in the actual process that may affect quality or its validation status

negative trend(s) in quality indicators

change(s) in the product design which affects the process

transfer of processes from one facility to another

change of the application of the process

The need for revalidation should be evaluated and documented. This evaluation should include historical results from quality indicators, product changes, process changes, changes in external requirements (regulations or standards) and other such circumstances.

Revalidation may not be as extensive as the initial validation if the situation does not require that all aspects of the original validation be repeated. If a new piece of equipment is purchased for a validated process, obviously the IQ portion of the validation needs to be repeated. However, most of the OQ aspects are already established. Some elements of PQ may need to be repeated, depending on the impact of the new equipment.

Another example might be if a raw material supplier is changed, the impact of that change on the process and resultant product should be considered. Parts of OQ and PQ might need to be redone, as the interaction between the new raw material and the process may not be fully understood.

7 Use of historical data for validation

Validation of a process can be partially based on accumulated historical manufacturing, testing, control, and other data related to a product or process. This historical data may be found in batch records, manufacturing log books, lot records, control charts, test and inspection results, customer feedback, field failure reports, service reports, and audit reports. A complete validation based on historical data is not feasible if all the appropriate data was not collected, or appropriate data was not collected in a manner which allows adequate analysis. Historical manufacturing data of a pass/fail nature is usually not adequate.

If historical data is determined to be adequate and representative, an analysis can be conducted per a written protocol to determine whether the process has been operating in a state of control and has consistently produced product which meets its predetermined requirements. The analysis should be documented.

The terms “retrospective validation”, “concurrent validation” and “prospective validation” are often used. Any validation can use historical data in the manner described above, regardless of the term used.

8 Summary of activities

Initial considerations include:

- Identify and describe the processes
- Decide on verification and/or validation
- Create a master validation plan

If the decision is to validate:

- Form multi-functional team for validation
- Plan the approach and define the requirements
- Identify and describe the processes
- Specify process parameters and desired output
- Create a master validation plan
- Select methods and tools for validation
- Create validation protocols
- Perform IQ, OQ, PQ and document results
- Determine continuous process controls
- Prepare final report and secure management approval

Control the process continuously

Maintaining a state of validation:

Monitor and control the process continuously

Revalidate as appropriate

Part 4:

CLEANING VALIDATION GUIDE

3.0 Principles

3.1 The objective of the cleaning validation is to verify the effectiveness of the cleaning procedure for removal of product residues, degradation products, preservatives, excipients and/or cleaning agents so that the analytical monitoring may be reduced to a minimum in the routine phase. In addition one needs to ensure there is no risk associated with cross-contamination of active ingredients.

3.2 Cleaning procedures must strictly follow carefully established and validated methods.

3.3 Appropriate cleaning procedures must be developed for all product-contact equipment used in the production process. Consideration should also be given to non-contact parts into which product may migrate, e.g., seals, flanges, mixing shaft, fans of ovens, heating elements etc.

3.4 Relevant process equipment cleaning validation methods are required for biological drugs because of their inherent characteristics (proteins are sticky by nature), parenteral product purity requirements, the complexity of equipment and the broad spectrum of materials which need to be cleaned.

3.5 Cleaning procedures for products and processes which are very similar do not need to be individually validated. This could be dependent on what is common, equipment and surface area, or an environment involving all product-contact equipment. It is considered acceptable to select a representative range of similar products and processes. The physical similarities of the products, the formulation, the manner and quantity of use by the consumer, the nature of other product previously manufactured, the size of batch in comparison to previously manufactured product are critical issues that justify a validation program. Health Canada Good Manufacturing Practices

A single validation study under consideration of the worst case can then be carried out which takes account of the relevant criteria. For biological drugs, including vaccines, bracketing may be considered acceptable for similar products and/or equipment provided appropriate justification, based on sound, scientific rationale is given. Some examples are cleaning of fermenters of the same design but with different vessel capacity used for the same type of recombinant proteins expressed in the same rodent cell line and cultivated in closely related growth media; a multi-antigen vaccine used to represent the individual antigen or other combinations of them when validating the same or similar equipment that is used at stages of formulation (adsorption) and/or holding. Validation of cleaning of fermenters should be done upon individual pathogen basis.

4.0 Validation of cleaning processes

4.1 As a general concept, until the validation of the cleaning procedure has been completed, the product contact equipment should be dedicated.

4.2 In a multi-product facility, the effort of validating the cleaning of a specific piece of equipment which has been exposed to a product and the cost of permanently dedicating the equipment to a single product should be considered.

4.3 Equipment cleaning validation may be performed concurrently with actual production steps during process development and clinical manufacturing. Validation programs should be continued through full scale commercial production.

4.4 It is usually not considered acceptable to test-until-clean. This concept involves cleaning, sampling and testing with repetition of this sequence until an acceptable residue limit is attained. For the system or equipment with a validated cleaning procedure, this practice of resampling should not be utilized.

4.5 Products which simulate the physicochemical properties of the substance to be removed may be considered for use instead of the substances themselves, when such substances are either toxic or hazardous.

4.6 Raw materials sourced from different suppliers may have different physical properties and impurity profiles. When applicable such differences should be considered when designing cleaning procedures, as the materials may behave differently.

4.7 All pertinent parameters should be checked to ensure the process as it will ultimately be run is validated. Therefore, if critical temperatures are needed to effect cleaning, then these should be verified. Any chemical agents added should be verified for type as well as quantity. Volumes of wash and rinse fluids, and velocity measurements for cleaning fluids should be measured as appropriate.

4.8 If automated procedures are utilized (Clean-In-Place: CIP), consideration should be given to monitoring the critical control points and the parameters with appropriate sensors and alarm points to ensure the process is highly controlled.

4.9 Validation of cleaning processes should be based on a worst-case scenario including:

(i) challenge of the cleaning process to show that the challenge soil can be recovered in sufficient quantity or demonstrate log removal to ensure that the cleaning process is indeed removing the soil to the required level, and

(ii) the use of reduced cleaning parameters such as overloading of contaminants, over drying of equipment surfaces, minimal concentration of cleaning agents and/or minimum contact time of detergents.

4.10 At least three (3) consecutive applications of the cleaning procedure should be performed and shown to be successful in order to prove that the method is validated.

5.0 Equipment and Personnel

5.1 All processing equipment should be specifically designed to facilitate cleanability and permit visual inspection and whenever possible, the equipment should be made of smooth surfaces of non-reactive materials.

5.2 Critical areas i.e. those hardest to clean should be identified, particularly in large systems that employ semiautomatic or fully automatic CIP systems.

5.3 Dedicated product-contact equipment should be used for products which are difficult to remove (e.g. tarry or gummy residues in the bulk 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. biologicals or products of high potency which may be difficult to detect below an acceptable limit).

5.4 In a bulk process, particularly for very potent chemicals such as some steroids, the issue of by-products needs to be considered if equipment is not dedicated.

5.5 It is difficult to validate a manual cleaning procedure, i.e. an inherently variable/cleaning procedure. Therefore, operators carrying out manual cleaning procedures should be adequately trained, monitored, and periodically assessed.

6.0 Microbiological considerations

6.1 Whether or not CIP systems are used for cleaning of processing equipment, microbiological aspects of equipment cleaning should be considered. This consists largely of preventive measures rather than removal of contamination once it has occurred.

6.2 There should be some documented evidence that routine cleaning and storage of equipment do not allow microbial proliferation. For example, equipment should be dried before storage, and under no circumstances should stagnant water be allowed to remain in equipment subsequent to cleaning operations. Time-frames for the storage of unclean equipment, prior to commencement of cleaning, as well as time frames and conditions for the storage of cleaned equipment should be established.

6.3 The control of the bio-burden through adequate cleaning and storage of equipment is important to ensure that subsequent sterilization or sanitization procedures achieve the necessary assurance of sterility. This is also particularly important from the standpoint of the control of pyrogens in sterile processing since equipment sterilization processes may not be adequate to achieve significant inactivation or removal of pyrogens.

7.0 Documentation

7.1 Detailed cleaning procedure(s) are to be documented in SOPs

7.2 A cleaning validation protocol should describe the procedure used to validate the cleaning process. It should include in addition to other information: description of the equipment used; interval between the end of production and the beginning of the cleaning procedures; cleaning procedures to be used for each product, each manufacturing system or each piece of equipment; sampling procedures with rationales; analytical methods including limit of detection and limit of quantitation; acceptance criteria with rationales and conditions for re-validation.

7.3 Depending upon the complexity of the system and cleaning processes, the amount of documentation necessary for executing various cleaning steps or procedures may vary.

7.4 When more complex cleaning procedures are required, it is important to document the critical cleaning steps. In this regard, specific documentation on the equipment itself which includes information about who cleaned it, when the cleaning was carried out, the product which was previously processed on the equipment being cleaned should be available. However, for relatively simple cleaning operations, the mere documentation that the overall cleaning process was performed might be sufficient.

7.5 Other factors such as history of cleaning, residue levels found after cleaning, and variability of test results may also dictate the amount of documentation required. For example, when variable residue levels are detected following cleaning, particularly for a process that is believed to be acceptable, one must establish the effectiveness of the process and of the operator performance. Appropriate evaluations must be made and when operator performance is deemed a problem, more extensive documentation (guidance) and training may be required.

8.0 Analytical methods

8.1 The analytical methods used to detect residuals or contaminants should be specific for the substance or the class of substances to be assayed (e.g., product residue, detergent residue and/or endotoxin) and be validated before the cleaning validation study is carried out.

8.2 The specificity and sensitivity of the analytical methods should be determined. If levels of contamination or residual are not detected, it does not mean that there is no residual contaminant present after cleaning,. It only means that the levels of contaminant greater than the sensitivity or detection limit of the analytical method are not present in the sample.

8.3 In the case of biological drugs, the use of product-specific assay(s) such as immunoassay(s) to monitor the presence of biological carry-over may not be adequate, a negative test may be the result of denaturation of protein epitope(s). Product-specific assay(s) can be used in addition to total organic carbon (TOC) for the detection of protein residue.

8.4 The analytical method and the percent recovery of contaminants should be challenged in combination with the sampling method(s) used (see below). This is to show that contaminants can be recovered from the equipment surface and to show the level of recovery as well as the consistency of recovery. This is necessary before any conclusions can be made based on the sample results. A negative test may also be the result of poor sampling technique.

How Clean Is Clean?

Cleaning Validation issues for Pharmaceutical Manufacturing

I. INTRODUCTION

Validation of cleaning procedures has generated considerable discussion since agency documents, including the Inspection Guide for Bulk Pharmaceutical Chemicals and the Biotechnology Inspection Guide, have briefly addressed this issue. These Agency documents clearly establish the expectation that cleaning procedures (processes) be validated.

One must recognize that for, as with validation of other processes, there may be more than one way to validate a process. In the end, the test of any validation process is whether scientific data shows that the system consistently does as expected and produces a result that consistently meets predetermined specifications.

II. PURPOSE OF CLEANING VALIDATION

The manufacture of pharmaceutical products requires a clean and sometimes even a sterile environment. Companies routinely implement contamination control programs to prevent introduction of physical, chemical and biological contaminants into their processing environment. These programs involve the cleaning of various types of surfaces in a systematic manner that is validated for effectiveness and monitored regularly. Recently, the cleanroom has become a more common means of addressing pharmaceutical sanitiation issues, and the uses of cleanrooms have become more diverse. It's important to remember, though, that appropriate cleaning materials and methods are essential to keep cleanrooms appropriately clean and to, in turn, make the manufactured product safer.

Contaminants enter cleanrooms and other critical process environments, or are generated within the room due to processes and personnel. Frequent, effective cleaning reduces the levels of contamination potentially transported to products by gas or liquid flow or by solid-solid contact. Cleaning the processing area is made more difficult by the variety of surfaces that need attention, which include curtains, walls, windows, floors, ceilings, table tops, and machinery with complicated inner and outer surfaces. A good general strategy is to make those areas closest to the product be the cleanest. Because cleaning materials become less clean in use, one should start with fresh materials near the product and clean toward the less clean areas.

Equally important as cleaning techniques and supplies, a sampling strategy must be devised for properly confirming and documenting cleanliness. The essential sampling and measurement issues that must be addressed include: Who is to do the sampling and analysis? What is to be measured (inputs and outputs)? When, where and how are the surfaces to be sampled (method, times, places) and analyzed? And, finally, why is the sampling being done? The sampling techniques used must also be compatible with the planned methods of analysis.

Validated sampling plans are particularly important now that cleaning validation is required by regulatory authority. Biomedical industries typically have requirements for validating cleaning to prove the efficacy of their methods.

Validation addresses the key issues of

what is being removed,

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the sampling methods that are used,

the analysis that is being done,

when evaluations are conducted,

the cleaning parameters that should be evaluated,

the final level of residuals that are acceptable, and on what basis, and the level of difficulty of the cleaning task.

"In the end, the test of any validation process is whether scientific data shows that the system consistently does as expected and produces a result that consistently meets predetermined specifications."

Regarding cleaning validation, the FDA "Guide to Inspections" says the sampling and analysis combination should be challenged to determine what fraction of the target material is actually sampled and then detected; and that direct sampling that is, with swabs is "most desirable," although rinse sampling may be satisfactory.

III. GENERAL REQUIREMENTS

The company should have written procedures (SOP's) detailing the cleaning processes used for various pieces of equipment. If firms have one cleaning process for cleaning between different batches of the same product and use a different process for cleaning between product changes, we expect the written procedures to address these different scenarios. Similarly, if firms have one process for removing water soluble residues and another process for non-water soluble residues, the written procedure should address both scenarios and make it clear when a given procedure is to be followed. Bulk pharmaceutical firms may decide to dedicate certain equipment for certain chemical manufacturing process steps that produce tarry or gummy residues that are difficult to remove from the equipment. Fluid bed dryer bags are another example of equipment that is difficult to clean and is often dedicated to a specific product. Any residues from the cleaning process itself (detergents, solvents, etc.) also have to be removed from the equipment.

firms to have written general procedures on how cleaning processes will be validated.

the general validation procedures to address who is responsible for performing and approving the validation study, the acceptance criteria, and when revalidation will be required.

firms to prepare specific written validation protocols in advance for the studies to be performed on each manufacturing system or piece of equipment which should address such issues as sampling procedures, and analytical methods to be used including the sensitivity of those methods.

firms to conduct the validation studies in accordance with the protocols and to document the results of studies.

a final validation report which is approved by management and which states whether or not the cleaning process is valid. The data should support a conclusion that residues have been reduced to an "acceptable level."

IV. EVALUATION OF CLEANING VALIDATION

The first step is to focus on the objective of the validation process, and we have seen that some companies have failed to develop such objectives. It is not unusual to see manufacturers use extensive sampling and testing programs following the cleaning process without ever really evaluating the effectiveness of the steps used to clean the equipment. Several questions need to be ad-

dressed when evaluating the cleaning process.

For example,

At what point does a piece of equipment or system become clean?

Does it have to be scrubbed by hand?

What is accomplished by hand scrubbing rather than just a solvent wash?

How variable are manual cleaning processes from batch to batch and product to product?

The answers to these questions are obviously important to the inspection and evaluation of the cleaning process since one must determine the overall effectiveness of the process. Answers to these questions may also identify steps that can be eliminated for more effective measures and result in resource savings for the company.

Determine the number of cleaning processes for each piece of equipment. Ideally, a piece of equipment or system will have one process for cleaning, however, this will depend on the products being produced and whether the cleanup occurs between batches of the same product (as in a large campaign) or between batches of different products. When the cleaning process is used only between batches of the same product (or different lots of the same intermediate in a bulk process) the firm need only meet a criteria of, "visibly clean" for the equipment. Such between batch cleaning processes do not require validation.

IV.1. Equipment Design

Examine the design of equipment, particularly in those large systems that may employ semi-automatic or fully automatic clean-in-place (CIP) systems since they represent significant concern. For example, sanitary type piping without ball valves should be used. When such nonsanitary ball valves are used, as is common in the bulk drug industry, the cleaning process is more difficult.

When such systems are identified, it is important that operators performing cleaning operations be aware of problems and have special training in cleaning these systems and valves. Determine whether the cleaning operators have knowledge of these systems and the level of training and experience in cleaning these systems. Also check the written and validated cleaning process to determine if these systems have been properly identified and validated.

In larger systems, such as those employing long transfer lines or piping, check the flow charts and piping diagrams for the identification of valves and written cleaning procedures. Piping and valves should be tagged and easily identifiable by the operator performing the cleaning function. Sometimes, inadequately identified valves, both on prints and physically, have led to incorrect cleaning practices.

Always check for the presence of an often critical element in the documentation of the cleaning processes; identifying and controlling the length of time between the end of processing and each cleaning step. This is especially important for topicals, suspensions, and bulk drug operations. In such operations, the drying of residues will directly affect the efficiency of a cleaning process.

Whether or not CIP systems are used for cleaning of processing equipment, microbiological aspects of equipment cleaning should be considered. This consists largely of preventive measures rather than removal of contamination once it has occurred. There should be some evidence that routine cleaning and storage of equipment does not allow microbial proliferation. For example, equipment should be dried before storage, and under no circumstances should stagnant water be allowed to remain in equipment subsequent to cleaningoperations.

Subsequent to the cleaning process, equipment may be subjected to sterilization or sanitization procedures where such equipment is used for sterile processing, or for nonsterile processing where

the products may support microbial growth. While such sterilization or sanitization procedures are beyond the scope of this guide, it is important to note that 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. This is also particularly important from the standpoint of the control of pyrogens in sterile processing since equipment sterilization processes may not be adequate to achieve significant inactivation or removal of pyrogens.

IV. 2. Written Cleaning Process (SOP for cleaning)

Examine the detail and specificity of the procedure for the (cleaning) process being validated, and the amount of documentation required. We have seen general SOPs, while others use a batch record or log sheet system that requires some type of specific documentation for performing each step. Depending upon the complexity of the system and cleaning process and the ability and training of operators, the amount of documentation necessary for executing various cleaning steps or procedures will vary.

When more complex cleaning procedures are required, it is important to document the critical cleaning steps (for example certain bulk drug synthesis processes). In this regard, specific documentation on the equipment itself which includes information about who cleaned it and when is valuable. However, for relatively simple cleaning operations, the mere documentation that the overall cleaning process was performed might be sufficient.

Other factors such as history of cleaning, residue levels found after cleaning, and variability of test results may also dictate the amount of documentation required. For example, when variable residue levels are detected following cleaning, particularly for a process that is believed to be acceptable, one must establish the effectiveness of the process and operator performance. Appropriate evaluations must be made and when operator performance is deemed a problem, more extensive documentation (guidance) and training may be required.

IV. 3. Analytical Methods

Determine the specificity and sensitivity of the analytical method used to detect residuals or contaminants. With advances in analytical technology, residues from the manufacturing and cleaning processes can be detected at very low levels. If levels of contamination or residual are not detected, it does not mean that there is no residual contaminant present after cleaning. It only means that levels of contaminant greater than the sensitivity or detection limit of the analytical method are not present in the sample. The firm should challenge the analytical method in combination with the sampling method(s) used to show that contaminants can be recovered from the equipment surface and at what level, i.e. 50% recovery, 90%, etc. This is necessary before any conclusions can be made based on the sample results. A negative test may also be the result of poor sampling technique (see below).

A typical cleaning validation study might employ pH, conductivity, total organic carbon, detergent assays, and if a multi-product facility, then a product-specific assay. Analyses should be compared for precision, accuracy, limits of detection, limits of quantitation, selectivity, linearity, range and sensitivity.

Several groups of researchers have conducted performance evaluations, matching common methods

high performance liquid chromatography (HPLC),

thin-layer chromatography (TLC),

UV spectrophotometry,

Fourier transform infrared (FTIR),

atomic absorption/ion chromatography

total organic carbon (TOC),

enzyme linked immunosorbent assay (ELISA),
enzymatic (ATP bioluminescence),
gel electrophoresis,
pH,
conductivity,
light microscopy,
gravimetric analysis,
titration,

Some have made a strong case for the use of the non-specific but highly sensitive TOC analysis for cleaning validation, noting that the technique has low-level detection (ppb), rapid analysis time, is low cost as compared to other methods, and can detect all carbon-based residuals. Others have selected TOC analysis in preference to total protein analysis formerly used for cleaning validation. Here, TOC analysis was applied successfully to cleaning validation for equipment used with water-soluble drugs, various excipients and cleaning agents.

Most cleaning validation work can be done using chemical or physical assays, but there are instances where biological assays are useful. Large flat surfaces can be sampled and the bioburden enumerated by contacting them with a sterile contact plate (RODAC plate) that contains solidified agar gel growth media. The plate is removed, incubated, and the number of colony-forming units determined. Flat surfaces and irregular surfaces can be swabbed with a sterile swab, then the material captured on the swab extracted into biological growth medium, incubated and the colony forming units counted.

IV. 4. Sampling Techniques

Start With Six Questions: The journalist's fundamental questions who, what, when, where, why and how are instructive with regard to sampling. The primary question is why the sampling is being done, which will help determine the answers to the other questions.

Why: The three main reasons to sample areas that will be cleaned or have been cleaned are: 1) to determine the initial contamination level and the degree of need for cleaning; 2) to determine the final contamination level remaining after cleaning; and 3) to determine the removal efficiency of a cleaning technique.

Who: Sampling should be done by production personnel under the supervision of the quality group. Adding non-production personnel to the area being sampled risks needless contamination and other disruptions to the processing routine.

What: Contamination levels to be measured include particles, microbes, product residues and cleaning agent residues. Samples are taken from surfaces, gases and liquids to reflect the levels of biological, chemical and particulate contamination.

When: Although cleaning can be scheduled strictly on the basis of time since the last cleaning or before the start of certain production changes, monitoring the contamination levels before cleaning and over time is informative with regard to the adequacy of the scheduling. The more frequent the sampling, the more informative the test results are.

Where: Sampling will be most informative in areas where the value of cleaning is greatest, namely near the product, in areas that are hard to clean and in representative areas, which are small areas that are similar to much larger areas of interest or are taken from a few instances out of a multitude of instances. Areas that are difficult to clean should be minimized in the design of the facility and

choice of equipment. This encompasses avoiding surfaces that are not smooth and flat; corners, depressions and knurled or roughened surfaces; areas that are a challenge to reach; porous regions; and heated regions, which are not easy to clean because they will accumulate material that has been in liquid that has subsequently evaporated, and because the usual increase of adhesion over time will be accelerated by heat. Unfortunately, areas that are hard to clean are often hard to sample well, too.

How Samples should be taken from a defined area (see Figures 2 and 3 on). Typically, partially overlapping parallel strokes are used. Where there are different surface textures in one direction versus another, a second sampling with partially overlapping strokes taken at right angles to the first may be advisable.

IV. 4. 1. Types of sampling:

There are two general types of sampling that have been found acceptable. The most desirable is the direct method of sampling the surface of the equipment. Another method is the use of rinse solutions.

The three major sampling methods for cleaning validation are

swabbing,

rinse sampling and

placebo sampling.

Each of these has benefits and drawbacks: swabs may remove more or less material than would likely be released in practice, for example, while placebo sampling may be more realistic than rinsing but more contaminating.

Factors that aid in removing contaminants also aid in sampling them, as long as interferences are avoided. Rinsing clearly requires a rinsing liquid, but swabbing is often done wet, too. Time, temperature, solvent concentration and affinity for the contaminant, detergency and mechanical energy all play roles. Deionized water alone is not likely to be adequate, except for highly soluble species that do not bind to the vessel. The constituents of the liquid must be chosen so as not to interfere with the analyses to be done. Such a liquid should also reduce surface tension, aid in dissolution of greases and oils, evaporate rapidly, leave minimal residue and not be toxic, flammable nor ozone-depleting. Clean alcohol added to water is a good choice, as alcohol lowers the surface tension to improve wetting, accelerates evaporation and can dissolve some hydrocarbons hardly soluble in water alone.

IV. 4. 1.a. Direct Surface Sampling –

Determine the type of sampling material used and its impact on the test data since the sampling material may interfere with the test. For example, the adhesive used in swabs has been found to interfere with the analysis of samples. Therefore, early in the validation program, it is important to assure that the sampling medium and solvent (used for extraction from the medium) are satisfactory and can be readily used.

Advantages of direct sampling are that areas hardest to clean and which are reasonably accessible can be evaluated, leading to establishing a level of contamination or residue per given surface area. Additionally, residues that are "dried out" or are insoluble can be sampled by physical removal.

Swabbing

A swab is a piece of fabric held by a handle; one can also use fabric held by tweezers, etc. The fabric and its holder must be very clean. The holder must be stiff enough to allow proper placement and pressure, and must be thick enough and suitably shaped or textured to be held easily but thin

enough to get into tight areas. Head and handle must be attached both cleanly and firmly.

Swabbing to sample has the advantage of physical removal of contaminants, but the swab and solvent must be chosen carefully and must not interfere with the analysis. Validation techniques depend in part on the surfaces to be cleaned. Flat surfaces are relatively easy to sample, and it is easy to determine how large an area has been sampled. One may be tempted to avoid corners and depressions, but often these areas need to be sampled, requiring small or pointed swabs. Areas that are hard to sample well are often also difficult to clean well, and they cannot be ignored. Even if swabbing is chosen, one may want to back up the technique with some rinsing, especially if there are areas swabs cannot reach.

Swab sampling should be done wearing gloves to minimize contamination. The area to be sampled should be clearly delineated and its dimensions recorded. If a template is used for swabbing, then it must not contaminate the sample. Some people make repeated passes, or repeated rinses, over the same area to increase the efficiency of removal.

Swabs should be moist but not saturated. Moist swabs pick up more material than dry swabs, but saturated swabs will leave behind more material than will moist swabs. The samples are obtained so as to have minimal extraneous contamination and to accumulate maximal amounts of contaminants, while being left accessible to the planned methods of analysis. An originally saturated swab head can be pressed against the inner surface of the vessel containing the swabbing solution in order to express some of the liquid. A level close to half the saturation value seems a plausible target. A used swab should not be allowed to contact the interior of the vessel holding the liquid, however. They should be stored cleanly, perhaps chilled to retard changes, while awaiting prompt analysis.

Some have noted that swabs are hard to use to sample the insides of equipment and that it is unclear how to combine swab results from nearly inaccessible locations with those from convenient, flat locations. One recommendation is to use rinse-fluid sampling if it can be shown to be adequate; otherwise, a combination of rinsing and swabbing should be used. A "guiding substance" should be chosen on which to base quantification. Recovery from swabs "spiked" with a guiding substance were found to be 92% to 99%, and the "limit of quantitation" at c.1 ng/cm2 of surface. Many such terms are defined in the Parenteral Drug Association (PDA) (1998) monograph.

Finally, one has to choose how much of which areas to sample. Guidelines published by a joint committee established by the International Pharmaceutical Federation (FIP, 1990), in addressing the validation and environmental monitoring of aseptic processing, included as options for sampling environmental surfaces either contact plates (25-50 cm2) or swabbing or rinsing, with limits (see below) generally placed on the basis of 25cm2 areas. The Recommended Practice RP-23 of the Institute of Environmental Sciences (IES, 1993) uses 25 cm2, too.

Combining Techniques

Because swabs supply solid-solid contact forces that can dislodge material that rinsing cannot, swabbing is generally preferable. Swabs sample what is left behind, while rinses indicate what is coming off. In some cases, regions that cannot be reached by swabs and that have to be sampled will require some form of rinsing, followed by capture and analysis of the contaminants. "Signal" and/or "noise" considerations could mandate rinsing. There may be cases where large areas having very low or highly non-uniform contamination would be better sampled by having a large area covered with a rinse, rather than having only a small fraction of the area sampled with swabbing. Finally, specific contaminants may require background levels in swabs that cannot currently be attained, but are obtainable in a rinse liquid.

Sample Recovery from Swabs

Recovery efficiency is the fraction of material originally present on the test surface that is subsequently quantified by the analysis. It involves removing the contaminant from the original surface,

extracting it from what was used to remove it, and measuring it. When swabs are used to remove the material, immersion in agitated liquid is used to extract it from the swab (see Figure 4). Researchers have found 60% to 170% recovery (at c. 10 µg) of E. coli protein using swabs having polyester heads to remove materials deposited on stainless steel with lyophilization. They found that swabs made of cotton glued to wood gave excessive absorbence and interference. Swabs with a polyester head that is heat bonded to a polymer handle are generally much cleaner than cotton glued to wood.

Ideally, to determine the recovery and analysis efficiency of a method, a known amount of contaminant of interest would be deposited on the surface just as in practice, then the surface would be swabbed, the swab extracted, the extract quantified, and the quantity thus found compared with the original, known amount. Alternatively, one measures material that is present due to practice. Lacking a reference method, one can use the usual method itself to estimate its own efficiency, through the technique of "exhaustive recovery," so that repetitive samples and extractions eventually recover all the material originally present. If the first sample gives a value N1 and immediately subsequent samples of the same region or material give values N2, N3, N4 and N5, then this series can be evaluated for convergence and the initial efficiency can be estimated as E = (N1) / (N1 + N2 + N3 + N4 + N5).

It should be noted that the ease of removal of a contaminant generally decreases with time, so that simulation tests should not only match the material of interest, but the method of deposition of interest and the typical conditions and duration between application and removal.

IV. 4. 1.b. Rinse Samples –

Two advantages of using rinse samples are that a larger surface area may be sampled, and inaccessible systems or ones that cannot be routinely disassembled can be sampled and evaluated.

A disadvantage of rinse samples is that the residue or contaminant may not be soluble or may be physically occluded in the equipment. An analogy that can be used is the "dirty pot." In the evaluation of cleaning of a dirty pot, particularly with dried out residue, one does not look at the rinse water to see that it is clean; one looks at the pot.

Check to see that a direct measurement of the residue or contaminant has been made for the rinse water when it is used to validate the cleaning process. For example, it is not acceptable to simply test rinse water for water quality (does it meet the compendia tests) rather than test it for potential contaminates.

IV. 4. 1. c. Routine Production In-Process Control

Monitoring - Indirect testing, such as conductivity testing, may be of some value for routine monitoring once a cleaning process has been validated. This would be particularly true for the bulk drug substance manufacturer where reactors and centrifuges and piping between such large equipment can be sampled only using rinse solution samples. Any indirect test method must have been shown to correlate with the condition of the equipment. During validation, the firm should document that testing the uncleaned equipment gives a not acceptable result for the indirect test.

How Much Sampling?

The frequency of sampling depends, in part, on how the limits for cleaning are determined, with some common options being fraction of a therapeutic dose allowed in a subsequently processed product; fraction of a toxic dose allowed in a subsequently processed product; limits of detection; or quantitation of the sampling/analysis methodology. For diagnostic products, the issues are safety and possible interferences. These considerations all have merit.

How much sampling needs to be done is determined by rules or by "engineering judgment."

Factors favoring more sampling include:

Improved estimation of mean levels (and their variability). Stochastic (probabilistic) standard error of the mean will decrease as 1/sqrt (number of samples, N). Deterministic error will decrease more rapidly, for example, in interpolation or calculation of the mean.

Reduced intervals (time or space) between determinations, during which changes may occur.

Improved sampling and analysis technique due to the "learning curve." Time per determination, expense, error follow various 1/Na relationships.

Demonstration of management's concern about what is being sampled.

Factors discouraging more sampling include:

Increased cost, due to wages, materials and use of analysis equipment. Fixed cost is unchanged, but variable cost will be in proportion to the amount done.

Increased possibility that sampling will contaminate. It is almost impossible to change only one thing, so that the act of sampling introduces changes that can cause problems.

Information overload, leading to loss of information or to information of lessened importance.

One important but frequently overlooked point is that, having sampled a surface, one needs to re-clean it because the sampling may well have contaminated the area. The analysis may indicate the surface was not sufficiently clean when sampled. Re-cleaning needs careful attention, following a rational standard operating procedure.

V. ESTABLISHMENT OF LIMITS

FDA does not intend to set acceptance specifications or methods for determining whether a cleaning process is validated. It is impractical for FDA to do so due to the wide variation in equipment and products used throughout the bulk and finished dosage form industries. The firm's rationale for the residue limits established should be logical based on the manufacturer's knowledge of the materials involved and be practical, achievable, and verifiable. It is important to define the sensitivity of the analytical methods in order to set reasonable limits. Some limits that have been mentioned by industry representatives in the literature or in presentations include analytical detection levels such as 10 PPM, biological activity levels such as 1/1000 of the normal therapeutic dose, and organoleptic levels such as no visible residue.

Check the manner in which limits are established. Unlike finished pharmaceuticals where the chemical identity of residuals are known (i.e., from actives, inactives, detergents) bulk processes may have partial reactants and unwanted by-products which may never have been chemically identified. In establishing residual limits, it may not be adequate to focus only on the principal reactant since other chemical variations may be more difficult to remove. There are circumstances where TLC screening, in addition to chemical analyses, may be needed. In a bulk process, particularly for very potent chemicals such as some steroids, the issue of by-products needs to be considered if equipment is not dedicated. The objective of the inspection is to ensure that the basis for any limits is scientifically justifiable.

VI. POINTS TO REMEMBER

Along with the essential elements discussed previously, there are several points to bear in mind when developing cleaning validation protocols:

Time from the end of manufacturing until the start of cleaning process. "It is critical to define an upper limit to this delay, because the time delay may change the nature of the residue to be cleanedit may dry out, for example." If the nature of the residue changes from what was used during validation, then the cleaning process may no longer be considered effective on that residue.

Time from the end of the cleaning process until the beginning of manufacture of the next batch. FDA looks closely at this since they are concerned about recontamination of the manufacturing equipment from environmental sources, or from microbial growth in wet equipment.

Water quality. Since considerations such as water hardness can affect detergent effectiveness, it is important to control the quality of the water used for cleaning. If tap water is used for cleaning, the validation runs should include at least one run at the upper limit of water hardness. In addition, "microbiological limits should be established for water used for rinsing, and a worst-case rinsing example should be included in one of the three validation runs," LeBlanc says.

Temperature control. If temperature is not controlled to a constant range during the cleaning process, then the temperature decay profile should be established, and perhaps monitored during routine production.

Worst-case examples. Validation should reflect a variety of worst-case examples. These worst cases should be within the normal operating parameters, and not worst cases assuming an out-of-control process. Examples include the lowest cleaning temperature, the lowest cleaning agent concentration, and the most difficult to clean areas (for residue sampling).

Grouping strategies. In a multi-product manufacturing environment, it would be costly to validate the cleaning of every product. Therefore, products manufactured in the same equipment may be grouped together, with one product chosen for cleaning validation applicable to all products in the group. "There should be some scientific rationale for grouping products togetherfor example, shampoos could be grouped together, or conditioners could be grouped," LeBlanc says. There should also be a rationale for selecting the representative example, which should typically be the most difficult-to-clean product. If the formulations varied significantly, then it may be necessary to have some laboratory data to select the most difficult-to-clean product.

CONCLUSION:

In summary, sampling and analysis help determine what your contamination concerns are and how well you are handling them. They are crucial to effective cleaning validation and monitoring, and thus deserve attention proportional to their, sometimes underestimated, importance.

	A PRAGMATIC APPROACH TO CLEANING VALIDATION
Step 1:	**Develop a cleaning validation plan**
	Defines the cleaning approach used at the facility
	Defines how validation activities will be conducted
	Defines the rationale for the validation approach
Step 2:	**Qualify the cleaning system (IQ, OQ)**
	Verify that the system is installed correctly and as specified (IQ testing)
	Verify that the system operates correctly and as specified (OQ testing)
	Check that the following are included: User Interface, Interlocks, Alarms, Monitoring/ Reporting, Sequence of Operation, CIP Sequence of Operations OQ Test
Step 3:	**Perform cycle development work (without product)**
	Establish soak times
	Establish rinse times
	Establish drain times
	Use rinse samples for pH and conductivity testing
	Use visual analysis
Step 4:	**Test cycle with product**
	Verify by visual examination, rinse analysis and limited swab analysis that the cycle is cleaning the equipment
	Soil the equipment with product
	Clean per normal procedures
	Sample rinse water for removal of cleaning agents and product
	Visually inspect and perform limited swabbing
Step 5:	**Perform PQ testing with product**
	Performance (or Process) Qualification studies are designed to demonstrate that a process, when performed per normal procedures, is ***consistently effective***.
	Consistency is demonstrated by successfully performing the studies three consecutive times.
	Effectiveness is demonstrated using a combination of analytical techniques, including rinse analysis, visual inspection and surface analysis (swabbing)
	Soil equipment with "worst case" conditions
	Perform visual inspection and swabbing on the "dirty" equipment
	Based upon previously established "map"
	Look for unexpected hard-to-clean areas
	Include visual inspection data
	Initiate cleaning cycle
	Sample initial rinse to establish the "starting point" of the residue limits
	Consider taking several samples over time to verify effective decay of soils
	Assay for water quality
	Assay for TOC (Total Organic Content) and Detergent
	Consider difficulty of sampling
	Sample during final rinse (both pre-and post-final rinse)
	Assay for incoming water quality
	Assay for TOC and Detergent
	Perform post cleaning swab and visual inspection
	Set Acceptance criteria
	Check that final rinse water meets incoming rinse water quality (including bioburden and endotoxin)
	1/1000 of a therapeutic dose of product A in product B
	Bioburden, Endotoxin, pH, Conductivity, TOC, Product and/or Detergent Specific, Filters, Rinse water analysis etc.
	Assay for previous product in rinse water