GUIDELINE ON GENERAL PRINCIPLES OF PROCESS VALIDATION

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GENERAL PRINCIPLES OF PROCESS VALIDATION

I. PURPOSE

This guideline outlines general principles that FDA considers to be acceptable elements of process validation for the preparation of human and animal drug products and medical devices.

II. SCOPE

This guideline is issued under Section 10.90 (21 CFR 10.90) and is applicable to the manufacture of pharmaceuticals and medical devices. It states principles and practices of general applicability that are not legal requirements but are acceptable to the FDA. A person may rely upon this guideline with the assurance of its acceptability to FDA, or may follow different procedures. When different procedures are used, a person may, but is not required to, discuss the matter in advance with FDA to prevent the expenditure of money and effort on activities that may later be determined to be unacceptable. In short, this guideline lists principles and practices which are acceptable to the FDA for the process validation of drug products and medical devices; it does not list the principles and practices that must, in all instances, be used to comply with law.

This guideline may be amended from time to time. Interested persons are invited to submit comments on this document and any subsequent revisions. Written comments should be submitted to the Dockets Management Branch (HFA-305), Food and Drug Administration, Room 4-62, 5600 Fishers Lane, Rockville, Maryland 20857. Received comments may be seen in that office between 9 a.m. and 4 p.m., Monday through Friday.

III. INTRODUCTION

Process validation is a requirement of the Current Good Manufacturing Practices Regulations for Finished Pharmaceuticals, 21 CFR Parts 210 and 211, and of the Good Manufacturing Practice Regulations for Medical Devices, 21 CFR Part 820, and therefore, is applicable to the manufacture of pharamaceuticals and medical devices.

Several firms have asked FDA for specific guidance on what FDA expects firms to do to assure compliance with the requirements for process validation. This guideline discusses process validation elements and concepts that are considered by FDA as acceptable parts of a validation program. The constituents of validation presented in this document are not intended to be all-inclusive. FDA recognizes that, because of the great variety of medical products (drug products and medical devices), processes and

manufacturing facilities, it is not possible to state in one document all of the specific validation elements that are applicable. Several broad concepts, however, have general applicability which manufacturers can use successfully as a guide in validating a manufacturing process. Although the particular requirements of process validation will vary according to such factors as the nature of the medical product (e.g., sterile vs non-sterile) and the complexity of the process, the broad concepts stated in this document have general applicability and provide an acceptable framework for building a comprehensive approach to process validation.

Definitions

Installation qualification - Establishing confidence that process equipment and ancillary systems are capable of consistently operating within established limits and tolerances.

Process performance qualification - Establishing confidence that the process is effective and reproducible.

Product performance qualification - Establishing confidence through appropriate testing that the finished product produced by a specified process meets all release requirements for functionality and safety.

Prospective validation - Validation conducted prior to the distribution of either a new product, or product made under a revised manufacturing process, where the revisions may affect the product's characteristics.

Retrospective validation - Validation of a process for a product already in distribution based upon accumulated production, testing and control data.

Validation - Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes.

Validation protocol - A written plan stating how validation will be conducted, including test parameters, product characteristics, production equipment, and decision points on what constitutes acceptable test results.

Worst case - A set of conditions encompassing upper and lower processing limits and circumstances, including those within standard operating procedures, which pose the greatest chance of process or product failure when compared to ideal conditions. Such conditions do not necessarily induce product or process failure.

IV. GENERAL CONCEPTS

Assurance of product quality is derived from careful attention to a number of factors including selection of quality parts and materials, adequate product and process design, control of the process, and in-process and end-product testing. Due to the complexity of today's medical products, routine end-product testing alone often is not sufficient to assure product quality for several reasons. Some end-product tests have limited sensitivity.[1] In some cases, destructive testing would be required to show that the manufacturing process was adequate, and in other situations end-product testing does not reveal all variations that may occur in the product that may impact on safety and effectiveness.[2]

The basic principles of quality assurance have as their goal the production of articles that are fit for their intended use. These

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1 For example, USP XXI states: "No sampling plan for applying sterility tests to a specified proportion of discrete units selected from a sterilization load is capable of demonstrating with complete assurance that all of the untested units are in fact sterile."

2 As an example, in one instance a visual inspection failed to detect a defective structural weld which resulted in the failure of an infant warmer. The defect could only have been detected by using destructive testing or expensive test equipment.

principles may be stated as follows: (1) quality, safety, and effectiveness must be designed and built into the product; (2) quality cannot be inspected or tested into the finished product; and (3) each step of the manufacturing process must be controlled to maximize the probability that the finished product meets all quality and design specifications. Process validation is a key element in assuring that these quality assurance goals are met.

It is through careful design and validation of both the process and process controls that a manufacturer can establish a high degree of confidence that all manufactured units from successive lots will be acceptable. Successfully validating a process may reduce the dependence upon intensive in-process and finished product testing. It should be noted that in most all cases, end-product testing plays a major role in assuring that quality assurance goals are met; i.e., validation and end-product testing are not mutually exclusive.

The FDA defines process validation as follows:

> Process validation is establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality characteristics.

It is important that the manufacturer prepare a written validation protocol which specifies the procedures (and tests) to be conducted and the data to be collected. The purpose for which data are collected must be clear, the data must reflect facts and be collected carefully and accurately. The protocol should specify a sufficient number of replicate process runs to demonstrate reproducibility and provide an accurate measure of variability among successive runs. The test conditions for these runs should encompass upper and lower processing limits and circumstances, including those within standard operating procedures, which pose the greatest chance of process or product failure compared to ideal conditions; such conditions have become widely known as "worst case" conditions. (They are sometimes called "most appropriate challenge" conditions.) Validation documentation should include evidence of the suitability of materials and the performance and reliability of equipment and systems.

Key process variables should be monitored and documented. Analysis of the data collected from monitoring will establish the variability of process parameters for individual runs and will establish whether or not the equipment and process controls are adequate to assure that product specifications are met.

Finished product and in-process test data can be of value in process validation, particularly in those situations where quality attributes and variabilities can be readily measured. Where finished (or in-process) testing cannot adequately measure certain attributes, process validation should be derived primarily from qualification of each system used in production and from consideration of the interaction of the various systems.

V. CGMP REGULATIONS FOR FINISHED PHARMACEUTICALS

Process validation is required, in both general and specific terms, by the Current Good Manufacturing Practice Regulations for Finished Pharmaceuticals, 21 CFR Parts 210 and 211. Examples of such requirements are listed below for informational purposes, and are not all-inclusive.

A requirement for process validation is set forth in general terms in section 211.100 — Written procedures; deviations — which states, in part:

> "There shall be written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess."

Several sections of the CGMP regulations state validation requirements in more specific terms. Excerpts from some of these sections are:

Section 211.110, Sampling and testing of in-process materials and drug products.

(a) "....control procedures shall be established to monitor the output and 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." (emphasis added)

Section 211.113, Control of Microbiological Contamination.

(b) "Appropriate written procedures, designed to prevent microbiological contamination of drug products purporting to be sterile, shall be established and followed. Such procedures shall include VALIDATION of any sterilization process." (emphasis added)

VI. GMP REGULATION FOR MEDICAL DEVICES

Process validation is required by the medical device GMP Regulations, 21 CFR Part 820. Section 820.5 requires every finished device manufacturer to:

"...prepare and implement a quality assurance program that is appropriate to the specific device manufactured..."

Section 820.3(n) defines quality assurance as:

"...all activities necessary to verify confidence in the quality of the process used to manufacture a finished device."

When applicable to a specific process, process validation is an essential element in establishing confidence that a process will consistently produce a product meeting the designed quality characteristics.

A generally stated requirement for process validation is contained in section 820.100:

"Written manufacturing specifications and processing procedures shall be established, implemented, and controlled to assure that the device conforms to its original design or any approved changes in that design."

Validation is an essential element in the establishment and implementation of a process procedure, as well as in determining what process controls are required in order to assure conformance to specifications.

Section 820.100(a)(1) states:

"...control measures shall be established to assure that the design basis for the device, components and packaging is correctly translated into approved specifications."

Validation is an essential control for assuring that the specifications for the device and manufacturing process are adequate to produce a device that will conform to the approved design characteristics.

VII. PRELIMINARY CONSIDERATIONS

A manufacturer should evaluate all factors that affect product quality when designing and undertaking a process validation study. These factors may vary considerably among different products and manufacturing technologies and could include, for example, component specifications, air and water handling systems, environmental controls, equipment functions, and process control operations. No single approach to process validation will be appropriate and complete in all cases; however, the following quality activities should be undertaken in most situations.

During the research and development (R&D) phase, the desired product should be carefully defined in terms of its characteristics, such as physical, chemical, electrical and

performance characteristics.[3] It is important to translate the product characteristics into specifications as a basis for description and control of the product.

Documentation of changes made during development provide traceability which can later be used to pinpoint solutions to future problems.

The product's end use should be a determining factor in the development of product (and component) characteristics and specifications. All pertinent aspects of the product which impact on safety and effectiveness should be considered. These aspects

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3 For example, in the case of a compressed tablet, physical characteristics would include size, weight, hardness, and freedom from defects, such as capping and splitting. Chemical characteristics would include quantitative formulation/potency; performance characteristics may include bioavailability (reflected by disintegration and dissolution). In the case of blood tubing, physical attributes would include internal and external diameters, length and color. Chemical characteristics would include raw material formulation. Mechanical properties would include hardness and tensile strength; performance characteristics would include biocompatibility and durability.

include performance, reliability and stability. Acceptable ranges or limits should be established for each characteristic to set up allowable variations.[4] These ranges should be expressed in readily measurable terms.

The validity of acceptance specifications should be verified through testing and challenge of the product on a sound scientific basis during the initial development and production phase.

Once a specification is demonstrated as acceptable it is important that any changes to the specification be made in accordance with documented change control procedures.

VIII. ELEMENTS OF PROCESS VALIDATION

A. Prospective Validation

Prospective validation includes those considerations that should be made before an entirely new product is introduced by a firm or when there is a change in the manufacturing process which may affect the product's characteristics, such as uniformity and identity. The following are considered as key elements of prospective validation.

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4 For example, in order to assure that an oral, ophthalmic, or parenteral solution has an acceptable pH, a specification may be established by which a lot is released only if it has been shown to have a pH within a narrow established range. For a device, a specification for the electrical resistance of a pacemaker lead would be established so that the lead would be acceptable only if the resistance was within a specified range.

1. Equipment and Process

The equipment and process(es) should be designed and/or selected so that product specifications are consistently achieved. This should be done with the participation of all appropriate groups that are concerned with assuring a quality product, e.g., engineering design, production operations, and quality assurance personnel.

a. Equipment: Installation Qualification

Installation qualification studies establish confidence that the process equipment and ancillary systems are capable of consistently operating within established limits and tolerances. After process equipment is designed or selected, it should be evaluated and tested to verify that it is capable of operating satisfactorily within the operating limits required by the process.[5] This phase of validation includes examination of equipment design; determination of calibration, maintenance, and adjustment requirements; and identifying critical equipment features that could affect the process and product. Information obtained from these studies should be used to establish written procedures covering equipment calibration, maintenance, monitoring, and control.

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5 Examples of equipment performance characteristics which may be measured include temperature and pressure of injection molding machines, uniformity of speed for mixers, temperature, speed and pressure for packaging machines, and temperature and pressure of sterilization chambers.

In assessing the suitability of a given piece of equipment, it is usually insufficient to rely solely upon the representations of the equipment supplier, or upon experience in producing some other product.[6] Sound theoretical and practical engineering principles and considerations are a first step in the assessment.

It is important that equipment qualification simulate actual production conditions, including those which are "worst case" situations.

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6 The importance of assessing equipment suitability based upon how it will be used to attain desired product attributes is illustrated in the case of deionizers used to produce Purified Water, USP. In one case, a firm used such water to make a topical drug product solution which, in view of its intended use, should have been free from objectionable microorganisms. However, the product was found to be contaminated with a pathogenic microorganism. The apparent cause of the problem was failure to assess the performance of the deionizer from a microbiological standpoint. It is fairly well recognized that the deionizers are prone to build-up of microorganisms—especially if the flow rates are low and the deionizers are not recharged and sanitized at suitable intervals. Therefore, these factors should have been considered. In this case, however, the firm relied upon the representations of the equipment itself, namely the "recharge" (i.e., conductivity) indicator, to signal the time for regeneration and cleaning. Considering the desired product characteristics, the firm should have determined the need for such procedures based upon pre-use testing, taking into account such factors as the length of time the equipment could produce deionized water of acceptable quality, flow rate, temperature, raw water quality, frequency of use, and surface area of deionizing resins.

Tests and challenges should be repeated a sufficient number of times to assure reliable and meaningful results. All acceptance criteria must be met during the test or challenge. If any test or challenge shows that the equipment does not perform within its specifications, an evaluation should be performed to identify the cause of the failure. Corrections should be made and additional test runs performed, as needed, to verify that the equipment performs within specifications. The observed variability of the equipment between and within runs can be used as a basis for determining the total number of trials selected for the subsequent performance qualification studies of the process.[7]

Once the equipment configuration and performance characteristics are established and qualified, they should be documented. The installation qualification should include a review of pertinent maintenance procedures, repair parts lists, and calibration methods for each piece of equipment. The objective is to assure that all repairs can be performed in such a way that will not affect the

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7 For example, the AAMI Guideline for Industrial Ethylene Oxide Sterilization of Medical Devices approved 2 December 1981, states: "The performance qualification should include a minimum of 3 successful, planned qualification runs, in which all of the acceptance criteria are met.....(5.3.1.2.).

characteristics of material processed after the repair. In addition, special post-repair cleaning and calibration requirements should be developed to prevent inadvertent manufacture a of non-conforming product. Planning during the qualification phase can prevent confusion during emergency repairs which could lead to use of the wrong replacement part.

b. Process: Performance Qualification

The purpose of performance qualification is to provide rigorous testing to demonstrate the effectiveness and reproducibility of the process. In entering the performance qualification phase of validation, it is understood that the process specifications have been established and essentially proven acceptable through laboratory or other trial methods and that the equipment has been judged acceptable on the basis of suitable installation studies.

Each process should be defined and described with sufficient specificity so that employees understand what is required.

Parts of the process which may vary so as to affect important product quality should be challenged.[8]

In challenging a process to assess its adequacy, it is important that challenge conditions simulate those that will be encountered during actual production, including "worst case" conditions. The challenges should be repeated enough times to assure that the results are meaningful and consistent.

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8 For example, in electroplating the metal case of an implantable pacemaker, the significant process steps to define, describe, and challenge include establishment and control of current density and temperature values for assuring adequate composition of electrolyte and for assuring cleanliness of the metal to be plated. In the production of parenteral solutions by aseptic filling, the significant aseptic filling process steps to define and challenge should include the sterilization and depyrogenation of containers/closures, sterilization of solutions, filling equipment and product contact surfaces, and the filling and closing of containers.

Each specific manufacturing process should be appropriately qualified and validated. There is an inherent danger in relying on what are perceived to be similarities between products, processes, and equipment without appropriate challenge.[9]

c. Product: Performance Qualification

For purposes of this guideline, product performance qualification activities apply only to medical devices. These steps should be viewed as pre-production quality assurance activities.

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9 For example, in the production of a compressed tablet, a firm may switch from one type of granulation blender to another with the erroneous assumption that both types have similar performance characteristics, and, therefore, granulation mixing times and procedures need not be altered. However, if the blenders are substantially different, use of the new blender with procedures used for the previous blender may result in a granulation with poor content uniformity. This, in turn, may lead to tablets having significantly differing potencies. This situation may be averted if the quality assurance system detects the equipment change in the first place, challenges the blender performance, precipitates a revalidation of the process, and initiates appropriate changes. In this example, revalidation comprises installation qualification of the new equipment and performance qualification of the process intended for use in the new blender.

Before reaching the conclusion that a process has been successfully validated, it is necessary to demonstrate that the specified process has not adversely affected the finished product. Where possible, product performance qualification testing should include performance testing under conditions that simulate actual use. Product performance qualification testing should be conducted using product manufactured from the same type of production equipment, methods and procedures that will be used for routine production. Otherwise, the qualified product may not be representative of production units and cannot be used as evidence that the manufacturing process will produce a product that meets the pre-determined specifications and quality attributes.[10]

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10 For example, a manufacturer of heart valves received complaints that the valve-support structure was fracturing under use. Investigation by the manufacturer revealed that all material and dimensional specifications had been met but the production machining process created microscopic scratches on the valve supporting wireform. These scratches caused metal fatigue and subsequent fracture. Comprehensive fatigue testing of production units under simulated use conditions could have detected the process deficiency.

In another example, a manufacturer recalled insulin syringes because of complaints that the needles were clogged. Investigation revealed that the needles were clogged by silicone oil which was employed as a lubricant during manufacturing. Investigation further revealed that the method used to extract the silicone oil was only partially effective. Although visual inspection of the syringes seemed to support that the cleaning method was effective, actual use proved otherwise.

After actual production units have sucessfully passed product performance qualification, a formal technical review should be conducted and should include:

- o Comparison of the approved product specifications and the actual qualified product.

- o Determination of the validity of test methods used to determine compliance with the approved specifications.

- o Determination of the adequacy of the specification change control program.

2. System to Assure Timely Revalidation

There should be a quality assurance system in place which requires revalidation whenever there are changes in packaging, formulation, equipment, or processes which could impact on product effectiveness or product characteristics, and whenever there are changes in product characteristics. Furthermore, when a change is made in raw material supplier, the manufacturer should consider subtle, potentially adverse differences in the raw material characteristics. A determination of adverse differences in raw material indicates a need to revalidate the process.

One way of detecting the kind of changes that should initiate revalidation is the use of tests and methods of analysis which are capable of measuring characteristics which may vary. Such tests and methods usually yield specific results which go beyond the mere pass/fail basis, thereby detecting variations within product and process specifications and allowing determination of whether a process is slipping out of control.

The quality assurance procedures should establish the circumstances under which revalidation is required. These may be based upon equipment, process, and product performance observed during the initial validation challenge studies. It is desirable to designate individuals who have the responsibility to review product, process, equipment and personnel changes to determine if and when revalidation is warranted.

The extent of revalidation will depend upon the nature of the changes and how they impact upon different aspects of production that had previously been validated. It may not be necessary to revalidate a process from scratch merely because a given circumstance has changed. However, it is important to carefully assess the nature of the change to determine potential ripple effects and what needs to be considered as part of revalidation.

3. Documentation

It is essential that the validation program is documented and that the documentation is properly maintained. Approval and release of the process for use in routine manufacturing should be based upon a review of all the validation documentation, including data from the equipment qualification, process performance qualification, and product/package testing to ensure compatibility with the process.

For routine production, it is important to adequately record process details (e.g., time, temperature, equipment used) and to record any changes which have occurred. A maintenance log can be useful in performing failure investigations concerning a specific manufacturing lot. Validation data (along with specific test data) may also determine expected variance in product or equipment characteristics.

B. Retrospective Process Validation

In some cases a product may have been on the market without sufficient premarket process validation. In these cases, it may be possible to validate, in some measure, the adequacy of the process by examination of accumulated test data on the product and records of the manufacturing procedures used.

Retrospective validation can also be useful to augment initial premarket prospective validation for new products or changed processes. In such cases, preliminary prospective validation

should have been sufficient to warrant product marketing. As additional data is gathered on production lots, such data can be used to build confidence in the adequacy of the process. Conversely, such data may indicate a declining confidence in the process and a commensurate need for corrective changes.

Test data may be useful only if the methods and results are adequately specific. As with prospective validation, it may be insufficient to assess the process solely on the basis of lot by lot conformance to specifications if test results are merely expressed in terms of pass/fail. Specific results, on the other hand, can be statistically analyzed and a determination can be made of what variance in data can be expected. It is important to maintain records which describe the operating characteristics of the process, e.g., time, temperature, humidity, and equipment settings.[11] Whenever test data are used to demonstrate conformance to specifications, it is important that the test methodology be qualified to assure that test results are objective and accurate.

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11 For example, sterilizer time and temperature data collected on recording equipment found to be accurate and precise could establish that process parameters had been reliably delivered to previously processed loads. A retrospective qualification of the equipment could be performed to demonstrate that the recorded data represented conditions that were uniform throughout the chamber and that product load configurations, personnel practices, initial temperature, and other variables had been adequately controlled during the earlier runs.

IX. ACCEPTABILITY OF PRODUCT TESTING

In some cases, a drug product or medical device may be manufactured individually or on a one-time basis. The concept of prospective or retrospective validation as it relates to those situations may have limited applicability, and data obtained during the manufacturing and assembly process may be used in conjunction with product testing to demonstrate that the instant run yielded a finished product meeting all of its specifications and quality characteristics. Such evaluation of data and product testing would be expected to be much more extensive than the usual situation where more reliance would be placed on prospective validation.

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