Guidance for Industry

Process Validation: General Principles and Practices

DRAFT GUIDANCE

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Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
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Center for Veterinary Medicine (CVM)

November 2008
Current Good Manufacturing Practices (CGMP)

Guidance for Industry

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I. INTRODUCTION

This guidance outlines the general principles and approaches that FDA considers to be appropriate elements of process validation for the manufacture of human and animal drug and biological products, including active pharmaceutical ingredients (API or drug substance), collectively referred to in this guidance as *drugs* or *products*. This guidance incorporates principles and approaches that all manufacturers can use in validating a manufacturing process.

This guidance aligns process validation activities with the product lifecycle concept and with existing FDA guidance.[2] The lifecycle concept links product and process development, qualification of the commercial manufacturing process, and maintenance of the process in a state of control during routine commercial production. This guidance promotes modern manufacturing principles, process improvement, innovation, and sound science.

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[1] This guidance has been prepared by the Division of Manufacturing and Product Quality, Center for Drug Evaluation and Research (CDER), in cooperation with the Center for Biologics Evaluation and Research (CBER) and the Center for Veterinary Medicine (CVM) at the Food and Drug Administration. FDA's Office of Regulatory Affairs (ORA) also contributed significantly to the development of this guidance.

[2] See the FDA/International Conference on Harmonisation (ICH) guidances for industry: Q8 Pharmaceutical Development, Q9 Quality Risk Management, and when finalized, Q10 Pharmaceutical Quality System (a notice of availability for the May 2007 ICH draft guidance, Q10 Pharmaceutical Quality System, published in the Federal Register on July 13, 2007 (72 FR 38604)). We update guidance documents periodically. To make sure you have the most recent version of a guidance, check the CDER guidance page at http://www.fda.gov/cder/guidance/index.htm, the CBER guidance page at http://www.fda.gov/cber/guidelines.htm, or the CVM guidance page at http://www.fda.gov/cvm/Guidance/published.htm.

The following categories of drugs are within the scope of this guidance:

- Human drugs
- Veterinary drugs
- Biological and biotechnology products
- Finished products and active pharmaceutical ingredients (API or drug substance)[3]
- The drug constituent of a combination (drug and medical device) product

The following categories of products are not covered by this guidance:

- Type A medicated articles and medicated feed
- Medical devices
- Dietary supplements
- Human tissues intended for transplantation regulated under section 361 of the Public Health Service Act[4]

This guidance does not specify what information should be included as part of a regulatory submission. Interested persons can refer to the appropriate guidance or contact the appropriate Center in determining what information should be included in a submission.

This guidance also does not specifically discuss the validation of automated process control systems (i.e., computer hardware and software interfaces), which are commonly integrated into modern drug manufacturing equipment. This guidance is relevant, however, to the validation of processes that include automated equipment in processing.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

In the *Federal Register* of May 11, 1987 (52 FR 17638), FDA issued a notice announcing the availability of a guidance entitled *Guideline on General Principles of Process Validation* (the

[3] Separate current good manufacturing practice (CGMP) regulations for drug components such as APIs (drug substances) and intermediates have not published as of the date of this guidance, but these components are subject to the statutory CGMP requirements of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 351(a)(2)(B)). Process validation for APIs is discussed in the FDA/ICH guidance for industry, *Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients* (ICH Q7A), available on the Internet at http://www.fda.gov/cder/guidance/index.htm. Section XII of ICH Q7A describes in detail the principles to be followed in validating API processes.

[4] See the FDA guidance for industry, *Validation of Procedures for Processing of Human Tissues Intended for Transplantation*, available on the Internet at http://www.fda.gov/cber/guidelines.htm.

1987 guidance).[5] Since then, we have obtained additional experience through our regulatory oversight that allows us to update our recommendations to industry on this topic. This revised guidance conveys FDA's current thinking on process validation and is consistent with basic principles first introduced in the 1987 guidance. This guidance also provides recommendations that reflect some of the goals of FDA's initiative entitled "Pharmaceutical CGMPs for the 21st Century – A Risk-Based Approach," particularly with regard to the use of technological advances in pharmaceutical manufacturing, as well as implementation of modern risk management and quality system tools and concepts. When finalized, this guidance will replace the 1987 guidance.

FDA has the authority and responsibility to inspect and evaluate process validation performed by manufacturers. The CGMP regulations for validating pharmaceutical (drug) manufacturing require that drug products be produced with a high degree of assurance of meeting all the attributes they are intended to possess (21 CFR 211.100(a) and 211.110(a)). Effective process validation contributes significantly to assuring drug quality. The basic principle of quality assurance is that a drug should be produced that is fit for its intended use; this principle incorporates the understanding that the following conditions exist:

- Quality, safety, and efficacy are designed or *built* into the product.
- Quality cannot be adequately assured merely by in-process and finished-product inspection or testing.
- Each step of a manufacturing process is controlled to assure that the finished product meets all design characteristics and quality attributes including specifications.

For purposes of this guidance, ***process validation*** **is defined as the collection and evaluation of data, from the process design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering quality products.** Process validation involves a series of activities taking place over the lifecycle of the product and process. This guidance describes the process validation activities in three stages.

- Stage 1 – Process Design: The commercial process is defined during this stage based on knowledge gained through development and scale-up activities.
- Stage 2 – Process Qualification: During this stage, the process design is confirmed as being capable of reproducible commercial manufacturing.
- Stage 3 – Continued Process Verification: Ongoing assurance is gained during routine production that the process remains in a state of control.

[5] The 1987 guidance was prepared by a working group that included representation from the Center for Devices and Radiological Health (CDRH). Since that time, CDRH elected to publish its own process validation guidance through the Global Harmonization Task Force. The principles and recommendations in that document, Quality Management Systems – Process Validation, edition 2 (available on the Internet at http://www.ghtf.org/sg3/sg3-final.html), are also useful to consider for drug manufacturing processes.

This guidance describes activities typical in each stage, but in practice, some activities in different stages might overlap.

Before any batch from the process is commercially distributed for use by consumers, a manufacturer should have gained *a high degree of assurance* in the performance of the manufacturing process such that it will consistently produce APIs and drug products meeting those attributes relating to identity, strength, quality, purity, and potency. The assurance should be obtained from objective information and data from laboratory-, pilot-, and/or commercial-scale studies. Information and data should demonstrate that the commercial manufacturing process is capable of consistently producing acceptable quality products within commercial manufacturing conditions, including those conditions that pose a high risk of process failure.

A successful validation program depends upon information and knowledge from product and process development. This knowledge and understanding is the basis for establishing an approach to control that is appropriate for the manufacturing process. Manufacturers should:

- understand the sources of variation
- detect the presence and degree of variation
- understand the impact of variation on the process and ultimately on product attributes
- control the variation in a manner commensurate with the risk it represents to the process and product

Each manufacturer should judge whether it has gained sufficient understanding to provide a high degree of assurance in its manufacturing process to justify commercial distribution of the product. Focusing on qualification efforts without understanding the manufacturing process may not lead to adequate assurance of quality. After establishing and confirming the process, manufacturers must maintain the process in a state of control over the life of the process, even as materials, equipment, production environment, personnel, and manufacturing procedures change.[6]

III. STATUTORY AND REGULATORY REQUIREMENTS FOR PROCESS VALIDATION

Process validation for drugs (finished pharmaceuticals and components) is a legally enforceable requirement under section 501(a)(2)(B) of the Act, which states the following:

> A drug . . . shall be deemed to be adulterated . . . if . . . the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to

[6] The statute and regulations described in section III of this guidance explain the requirement that the methods and facilities used for the manufacturing of drugs be operated and maintained under control sufficient to assure that the identity, strength, purity, and quality of a drug are as they purport or are represented to possess.

> safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess.

FDA regulations describing current good manufacturing practice (CGMP) are provided in 21 CFR parts 210 and 211.

Process validation is required, in both general and specific terms, by the CGMP regulations in parts 210 and 211. The foundation for process validation is provided in § 211.100(a), which states that "[t]here 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" (emphasis added). This regulation requires that manufacturers design a process including operations and controls that will result in a product meeting these attributes. *Product quality* in the context of process validation means that product performance is consistent from batch-to-batch and unit-to-unit. Many products are single-source or involve complicated processes to manufacture. Validation also offers assurance that a process is reasonably safeguarded from sources of variability affecting production output, the loss of which can cause supply problems, thereby negatively affecting public health.

Other CGMP regulations define the various aspects of validation. Section 211.110(a), *Sampling and testing of in-process materials and drug products*, requires that control procedures ". . . 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" (emphasis added). This regulation establishes the requirement that even well-designed processes must include in-process control procedures to assure final product quality.

CGMP regulations require that batch samples represent the batch under analysis (see, e.g., § 211.160(b)(3)) and that the sampling plan result in statistical confidence (§ 211.165(c) and (d)) that the batch meets its predetermined specifications (§ 211.165(a)). Section 211.110(b) provides two principles to follow when establishing in-process specifications. The first principle is that ". . . in-process specifications for such characteristics [of in-process material and the drug product] shall be consistent with drug product final specifications . . . ." Accordingly, in-process material should be controlled to assure that the final drug product will meet its quality requirements. The second principle in this regulation further requires that in-process specifications ". . . 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." This requirement, in part, establishes the need for manufacturers to analyze process performance and control batch-to-batch variability.[7]

[7] In the *Federal Register* of September 29, 1978 (43 FR 45013 at 45052), FDA published a final rule on "Current Good Manufacturing Practice in Manufacture, Processing, Packing, or Holding" (available on the Internet at http://www.fda.gov/cder/dmpq/preamble.txt). In the preamble of the final rule, the Agency further explains this principle.

The CGMP regulations also describe and define activities connected with process design, development, and maintenance. Section 211.180(e) requires that information and data about product performance and manufacturing experience be periodically reviewed to determine whether any changes to the established process are warranted. Ongoing feedback about product performance is an essential feature of process maintenance.

In addition, the CGMP regulations require that facilities in which drugs are manufactured be of suitable size, construction, and location to facilitate proper operations (21 CFR 211.42). Equipment must be of appropriate design, adequate size, and suitably located to facilitate operations for its intended use (21 CFR 211.63). Automated, mechanical, and electronic equipment must be calibrated, inspected, or checked according to a written program designed to assure proper performance (21 CFR 211.68).

In summary, the CGMP regulations require that manufacturing processes be designed and controlled to assure that in-process materials and the finished product meet predetermined quality requirements and do so consistently and reliably.

IV. RECOMMENDATIONS

A. General Considerations for Process Validation

In all stages of the product lifecycle, good project management and good archiving that capture scientific knowledge will make the process validation program more effective and efficient. These practices should ensure uniform collection and assessment of information about the process, reduce the chance for redundant information gathering and analysis, and enhance the accessibility of such information later in the product lifecycle.

We recommend an integrated[8] team approach to process validation that includes expertise from a variety of disciplines, including process engineering, industrial pharmacy, analytical chemistry, microbiology, statistics, manufacturing, and quality assurance. Project plans, along with the full support of senior management, are essential elements for success.

Throughout the product lifecycle, various studies can be initiated to discover, observe, correlate, or confirm information about the product and process. All studies should be planned and conducted according to sound scientific principles, appropriately documented, and should be approved in accordance with the established procedure appropriate for the stage of the lifecycle.

B. Specific Stages and Activities of Process Validation in the Product Lifecycle

The following subsections describe the recommended stages and specific activities.

[8] This concept is discussed in more detail in FDA's guidance for industry, *Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations*, available on the Internet at http://www.fda.gov/cder/guidance/index.htm.

1. Stage 1 – Process Design

a. Building and Capturing Process Knowledge and Understanding

Process design is the activity of defining the commercial manufacturing process that will be reflected in the master production and control records. The goal of this stage is to design a process suitable for routine commercial manufacturing that can consistently deliver a product that meets its critical quality attributes.

Generally, early process design experiments do not need to be performed under CGMP conditions. They should, however, be conducted in accordance with sound scientific methods and principles, including good documentation practices. This recommendation is consistent with ICH guidance for industry, *Q10 Pharmaceutical Quality System*.[9] Decisions and justification of the controls should be sufficiently documented and internally reviewed to verify and preserve their value for use later in the lifecycle of the process and product.

There are exceptions, however. For example, viral and impurity clearance studies have a direct impact on drug safety and should be performed under CGMP conditions, even when performed at small scale. The quality unit should be involved with these studies as is typical during commercial production.

Product-development activities provide key inputs to the design stage, such as the intended dosage form, the quality attributes, and a general manufacturing pathway. Process information available from the product-development stage can be leveraged in the process-design stage. However, the full spectrum of input variability typical of commercial production is not generally known at this stage. The functionality and limitations of commercial manufacturing equipment should be considered, as well as the contributions of variability by different component lots, production operators, environmental conditions, and measurement systems in the production setting. Laboratory or pilot-scale models designed to be representative of the commercial process can be used to estimate variability. However, it is not a regulatory expectation that the process be developed and tested until it fails, but rather that a process be controlled within commercial manufacturing conditions, including those combinations of conditions posing a high risk of process failure.

Designing an efficient process with an effective process control approach is dependent on the process knowledge and understanding obtained. Design of Experiment (DOE) studies can help develop process knowledge by revealing relationships, including multifactorial interactions, between the variable inputs (e.g., component[10] characteristics

[9] A notice of availability for this draft ICH guidance published in the *Federal Register* on July 13, 2007 (72 FR 38604). When finalized, this guidance will represent FDA's current thinking on this topic.

[10] "*Component* means any ingredient [raw material] intended for use in the manufacture of a drug product, including those that may not appear in such drug product" (21 CFR 210.3(b)(3)).

or processing parameters) and the resulting outputs (e.g., in-process material, intermediates, or the final product). Risk analysis tools can be used to screen potential variables for DOE studies to minimize the total number of experiments conducted while maximizing knowledge gained. The results of DOE studies can provide justification for establishing ranges of incoming component quality, equipment parameters, and in-process material quality attributes.

Other activities, such as experiments or demonstrations at laboratory or pilot scale, allow evaluation of certain conditions and prediction of performance of the commercial process. These activities also provide information that can be used to model or simulate the commercial process. Computer-based or virtual simulations of certain unit operations or dynamics can provide process understanding and avoid problems at commercial scale. It is important to understand the degree to which models represent the commercial process, including any differences that might exist, as this may have an impact on the relevance of information derived from the studies.

It is essential that activities and studies resulting in product understanding be documented. Documentation should reflect the basis for decisions made about the process. For example, manufacturers should document the variables studied for a unit operation and the rationale for those variables identified as significant. This information is useful during the process qualification and continued process verification stages, including when the design is revised or the strategy for control is refined or changed.

b. Establishing a Strategy for Process Control

Process knowledge and understanding is the basis for establishing an approach to process control for each unit operation and the process overall. Strategies for process control can be designed to reduce input variation, adjust for input variation during manufacturing (and so reduce its impact on the output), or combine both approaches.

Process controls address variability to assure quality of the product. Controls can consist of material analysis and equipment monitoring at significant processing points designed to assure that the operation remains on target and in control with respect to output quality. Special attention to control of the process through operational limits and in-process monitoring is essential (1) where the product attribute is not readily measurable due to limitations of sampling or detectability (e.g., viral clearance or microbial contamination), or (2) when intermediates and products cannot be highly characterized and well-defined quality attributes cannot be identified. These controls are included in the master production and control records (see 21 CFR 211.186(a) and (b)(9)).

More advanced strategies, such as process analytical technology (PAT), use timely analysis and control loops to adjust the processing conditions so that the output remains constant. Manufacturing systems of this type can provide a higher degree of process control. In the case of PAT strategy, the approach to process qualification will be different from that for other process designs. Further information on PAT processes can

be found in FDA's guidance for industry on *PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance* (available on the Internet at http://www.fda.gov/cder/guidance/index.htm).

The planned commercial production and control records, which contain the operational limits and overall strategy for process control, should be carried forward to the next stage for confirmation.

2. Stage 2 – Process Qualification

During the process qualification stage of process validation, the process design is confirmed as being capable of reproducible commercial manufacture. This stage has two elements: (1) design of the facility and qualification of the equipment and utilities, and (2) performance qualification (PQ). During this stage, CGMP-compliant procedures must be followed and successful completion of this stage is necessary before commercial distribution.[11] Products manufactured during this stage, if acceptable, can be released.

a. Design of a Facility and Qualification of Utilities and Equipment

Proper design of a manufacturing facility is required under 21 CFR part 211, subpart C, of the CGMP regulations on *Buildings and Facilities*. It is essential that activities performed to assure proper facility design and commissioning precede PQ. Activities undertaken to demonstrate that utilities and pieces of equipment are suitable for their intended use and perform properly is referred to in this guidance as *qualification*. These activities necessarily precede manufacturing products at the commercial scale.

Qualification of utilities and equipment generally includes the following activities:

- Selecting utilities and equipment construction materials, operating principles, and performance characteristics based on whether they are appropriate for their specific use.

- Verifying that utility systems and equipment are built and installed in compliance with the design specifications (e.g., built as designed with proper materials, capacity, and functions, and properly connected and calibrated).

- Verifying that the utility system and equipment operate in accordance with the process requirements in all anticipated operating ranges. This should include challenging the equipment or system functions while under load comparable to that expected during routine production. It should also include the performance of interventions, stoppage, and start-up as is expected during routine production.

[11] As discussed in section III of this guidance, process validation (including process qualification) is legally enforceable under section 501(a)(2)(B) of the Act. FDA regulations require that process validation procedures be established and followed (21 CFR 211.100) before a batch can be distributed (21 CFR 211.22 and 211.165).

Operating ranges should be shown capable of being held as long as would be necessary during routine production.

Qualification of utilities and equipment can be covered under individual plans or as part of an overall project plan. The plan should consider the requirements of use and can incorporate risk management to prioritize certain activities and to identify a level of effort in both the performance and documentation of qualification activities. The plan should identify (1) the studies or tests to use, (2) the criteria appropriate to assess outcomes, (3) the timing of qualification activities, (4) responsibilities, and (5) the procedures for documenting and approving the qualification. It should also include the firm's requirements for the evaluation of changes. Qualification activities should be documented and summarized in a report with conclusions that address criteria in the plan. The quality control unit must review and approve the qualification plan and report (21 CFR 211.22).

b. Performance Qualification Approach

The PQ is the second element of stage 2, process qualification. The PQ combines the actual facility, utilities, equipment (each now qualified), and the trained personnel with the commercial manufacturing process, control procedures, and components to produce commercial batches. A successful PQ will confirm the process design and demonstrate that the commercial manufacturing process performs as expected.

Success at this stage signals an important milestone in the product lifecycle and needs to be completed before a manufacturer commences commercial distribution of the drug product.[12] The decision to begin commercial distribution should be supported by data from commercial batches. Data from laboratory and pilot studies can provide additional assurance.

The approach to PQ should be based on sound science and the manufacturer's overall level of product and process understanding. The cumulative data from all relevant studies (e.g., designed experiments; laboratory, pilot, and commercial batches) should be used to establish the manufacturing conditions in the PQ. For example, to have sufficient understanding of the commercial process, the manufacturer will need to consider the effects of scale; however, it is not typically necessary to explore the entire operating range at commercial scale if assurance can be provided by other data. Previous credible experience with sufficiently similar products and processes can also be considered. In addition, we strongly recommend firms employ objective measures (e.g., statistical metrics), wherever feasible and meaningful to achieve adequate assurance.

In most cases, PQ will have a higher level of sampling, additional testing, and greater scrutiny of process performance. The level of monitoring and testing should be sufficient to confirm uniform product quality throughout the batch during processing. This greater

[12] See section III of this guidance, Statutory and Regulatory Requirements for Process Validation.

scrutiny accompanied by a higher level of sampling should continue through the process verification stage, as appropriate.

The extent to which some materials, such as column resins or molecular filtration media, can be re-used without adversely affecting product quality can be assessed in relevant laboratory studies, and their usable lifetime should be confirmed by an ongoing PQ protocol during commercial manufacture.

A manufacturing process that uses PAT may warrant a different PQ approach. Such a process is one that is designed to measure in real time the attributes of an in-process material and then adjust the process in a timely control loop so the process maintains the desired quality of the output material. The process design stage and the process qualification stage should have as a focus the measurement system and control loop. Regardless, the goal remains the same: establishing scientific evidence that the process is reproducible and will consistently deliver quality products.

c. Performance Qualification Protocol

A written protocol that specifies the manufacturing conditions, controls, testing, and expected outcomes is essential for this stage of process validation. We recommend that the protocol discuss:

- The manufacturing conditions including operating parameters, processing limits, and component (raw material) inputs.

- The data to be collected and when and how it will be evaluated.

- Tests to be performed (in-process, release, characterization) and acceptance criteria for each significant processing step.

- The sampling plan including sampling points, number of samples, and the frequency of sampling for each unit operation and attribute. The number of samples should be adequate to provide sufficient statistical confidence of quality both within a batch and between batches. The confidence level selected can be based on risk analysis as it relates to the particular attribute under examination. Sampling during this stage should be more extensive than is typical during routine production.

- Criteria that provide for a rational conclusion of whether the process consistently produces quality products. The criteria should include:

    - A description of the statistical methods to be used in analyzing all collected data (e.g., statistical metrics defining both intra-batch and inter-batch variability).

- Provision for addressing deviations from expected conditions and handling of nonconforming data. Data should not be excluded from further consideration in terms of PQ without a documented, science-based justification.

- Design of facilities and the qualification of utilities and equipment, personnel training and qualification, and verification of material sources (components and container/closures), if not previously accomplished.

- Status of the validation of analytical methods used in measuring the process, in-process materials, and the product.

- Review and approval by appropriate departments and the quality unit.

d. Protocol Execution and Report

Protocol execution should not begin until the protocol has been reviewed and approved by all appropriate departments, including the quality unit. Departure from the established protocol must be made according to established procedure or provisions in the protocol. Such departures must be justified and approved by all appropriate departments and the quality unit before implementation (§ 211.100).

The commercial manufacturing process and routine procedures must be followed (§§ 211.100(b) and 211.110(a)). The PQ lots should be manufactured under normal conditions by personnel expected to routinely perform each step of each unit operation in the process. Normal operating conditions should cover the utility systems (e.g., air handling and water purification), material, personnel, environment, and manufacturing procedures.

A report documenting and assessing adherence to the written protocol should be prepared in a timely manner after the completion of the protocol. This report should:

- Discuss and cross-reference all aspects of the protocol.

- Summarize data collected and analyze the data, as specified by the protocol.

- Evaluate any unexpected observations and additional data not specified in the protocol.

- Summarize and discuss all manufacturing nonconformances such as deviations, aberrant test results, or other information that has bearing on the validity of process.

- Describe in sufficient detail any corrective actions or changes that should be made to existing procedures and controls.

- State a clear conclusion as to whether the data indicates the process met the conditions established in the protocol and whether the process is considered to be in a sufficient state of control. If not, the report should state what should be accomplished before such a conclusion can be reached. This conclusion should be based on a documented justification for the approval of the process, and release of lots produced by it to the market in consideration of the entire compilation of knowledge and information gained from the design stage through the process qualification stage.

- Include all appropriate department and quality unit review and approvals.

3. Stage 3 – Continued Process Verification

The goal of the third validation stage is to continually assure that the process remains in a state of control (the validated state) during commercial manufacture. A system or systems for detecting unplanned departures from the process as designed is essential to accomplish this goal. Adherence to the CGMP requirements, specifically including the collection and evaluation of information and data about the performance of the process (see below), will allow detection of process *drift*. The evaluation should determine whether action must be taken to prevent the process from drifting out of control (§ 211.180(e)).

An ongoing program to collect and analyze product and process data that relate to product quality must be established (§ 211.180(e)). The data collected should include relevant process trends and quality of incoming materials or components, in-process material, and finished products. The data should be statistically trended and reviewed by trained personnel. The information collected should verify that the critical quality attributes are being controlled throughout the process.

We recommend that a statistician or person with adequate training in statistical process control techniques develop the data collection plan and statistical methods and procedures used in measuring and evaluating process stability and process capability. Procedures should describe how trending and calculations are to be performed. Procedures should guard against overreaction to individual events as well as against failure to detect process drift. Production data should be collected to evaluate process stability and capability. The quality unit should review this information. If done properly, these efforts can identify variability in the process and/or product; this information can be used to alert the manufacturer that the process should be improved.

Good process design and development should anticipate significant sources of variability and establish appropriate detection, control, and/or mitigation strategies, as well as appropriate alert and action limits. However, a process is likely to encounter sources of variation that were not previously detected or to which the process was not previously exposed. Many tools and techniques, some statistical and others more qualitative, can be used to detect variation, characterize it, and determine the root cause. We recommend that the manufacturer use quantitative, statistical methods whenever feasible. We also

recommend that it scrutinize intra-batch as well as inter-batch variation as part of a comprehensive *continued process verification* program.

We recommend continued monitoring and/or sampling at the level established during the process qualification stage until sufficient data is available to generate significant variability estimates. Once the variability is known, sampling and/or monitoring should be adjusted to a statistically appropriate and representative level. Process variability should be periodically assessed and sampling and/or monitoring adjusted accordingly.

Variation can also be detected by the timely assessment of defect complaints, out-of-specification findings, process deviation reports, process yield variations, batch records, incoming raw material records, and adverse event reports. Production line operators and quality unit staff should be encouraged to provide feedback on process performance. Operator errors should also be tracked to measure the quality of the training program; to identify operator performance issues; and to look for potential batch record, procedural, and/or process improvements that could help to reduce operator error. We recommend that the quality unit meet periodically with production staff to evaluate data, discuss possible trends or drifts in the process, and coordinate any correction or follow-up actions by production.

Data gathered during this stage might suggest ways to improve and/or optimize the process by altering some aspect of the process or product such as the operating conditions (ranges and set-points), process controls, component, or in-process material characteristics. A description of the planned change, a well-justified rationale for the change, an implementation plan, and quality unit approval before implementation must be documented (21 CFR 211.100). Depending on the significance to product quality, modifications may warrant performing additional process design and process qualification activities.[13]

Maintenance of the facility, utilities, and equipment is another important aspect of ensuring that a process remains in control. Once established, qualification status must be maintained through routine monitoring, maintenance, and calibration procedures and schedules (21 CFR part 211, subparts C and D). The data should be assessed periodically to determine whether re-qualification should be performed and the extent of that re-qualification. Maintenance and calibration frequency should be adjusted based on feedback from these activities.

V. CONCURRENT RELEASE OF PERFORMANCE QUALIFICATION BATCHES

In most cases, the PQ protocol needs to be completed before the commercial distribution of a product. In special situations, the PQ protocol can be designed to release a PQ batch for

[13] Certain manufacturing changes may call for a formal notification to the Agency before implementation, as directed by existing regulations and *filing* guidance (i.e., documents that describe procedures for filing information to an application).

distribution before completion of the protocol. The conclusions about the manufacturing process should be made when the protocol is completed and the data is fully evaluated.

FDA expects that concurrent release will be used rarely. Concurrent release might be appropriate for processes used infrequently because of limited demand for the product (e.g., orphan drugs), processes with necessarily low production volume per batch (e.g., radiopharmaceuticals, including positron emission tomography drugs), and processes manufacturing *medically necessary* drugs to alleviate a short supply, which should be coordinated with the Agency.

When warranted and used, concurrent release should be accompanied by a system for careful oversight of the distributed batch to facilitate rapid customer feedback. For example, customer complaints and defect reports should be rapidly assessed to determine root cause and whether the process should be improved or changed. We recommend that each batch in a concurrent release program also undergo stability testing and that this test data be promptly evaluated to ensure rapid detection and correction of any problems.

VI. DOCUMENTATION

Documentation at each stage of the process validation lifecycle is essential for effective communication in complex, lengthy, and multidisciplinary projects. Documentation is important so that knowledge gained about a product and process is accessible and comprehensible to others involved in each stage of the lifecycle. In addition to being a fundamental tenet of following the scientific method, information transparency and accessibility are essential so that organizational units responsible and accountable for the process can make informed, science-based decisions that ultimately support the release of a product to commerce.

The degree and type of documentation required by CGMP is greatest during stage 2, process qualification, and stage 3, continued process verification. Studies during these stages must conform to CGMPs and must be approved by the quality unit in accordance with the regulations (see 21 CFR 211.22 and 211.100). Viral and impurity clearance studies, even when performed at small scale, also require full quality unit oversight as is necessary during routine commercial production.

CGMP documents for commercial manufacturing (i.e., the initial commercial master batch production and control record (21 CFR 211.186) and supporting procedures) are key outputs of stage 1, process design. We recommend that firms diagram the process flow for the full-scale process. Process flow diagrams should describe each unit operation, its placement in the overall process, monitoring and control points, and the component, as well as other processing material inputs (e.g., processing aids) and expected outputs (i.e., in-process materials and finished product). It is also useful to generate and preserve process flow diagrams of the various scales as the process design progresses to facilitate comparison and decision making about their comparability.

VII. ANALYTICAL METHODOLOGY

Process knowledge is dependent on accurate and precise measuring techniques that are used to test and examine the quality of drug components, in-process materials, and finished products. For data to have value in predicting process outcomes, it is essential that the analytical tests be scientifically sound (as required under 21 CFR 211.160). While validated analytical methods are not required during product- and process-development activities, methods should be scientifically sound (e.g., specific, sensitive, and accurate), suitable, and reliable for the specified purpose. There should be assurance of proper equipment function for laboratory experiments. Procedures for analytical method and equipment maintenance, documentation practices, and calibration practices supporting process-development efforts should be documented or described. Analytical methods supporting clinical supply production, particularly stage 2 and 3 studies, must follow appropriate CGMPs in parts 210 and 211.

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