Guidance for Industry
Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations

DRAFT GUIDANCE

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Pharmaceutical CGMPs

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Guidance for Industry[1]

Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This draft guidance is intended to help manufacturers that are implementing modern quality systems and risk management approaches to meet the requirements of the Agency's current good manufacturing practice (CGMP) regulations (2l CFR parts 210 and 211). The guidance describes a *comprehensive quality systems (QS) model*, highlighting the model's consistency with the CGMP regulatory requirements for manufacturing human and veterinary drugs, including biological drug products. The guidance also explains how manufacturers implementing such quality systems can be in full compliance with parts 210 and 211. This guidance is not intended to place new expectations on manufacturers nor to replace the CGMP requirements. Readers are advised to always refer to parts 210 and 211 to ensure full compliance with the regulations.

FDA's guidance documents, including this draft guidance, do not establish legally enforceable responsibilities.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 AND PURPOSE

A. Background

In August 2002, the FDA announced the Pharmaceutical CGMPs for the 21st Century Initiative. In that announcement, the FDA explained the Agency’s intent to integrate *quality systems* and *risk management* approaches into existing programs with the goal of encouraging the adoption of modern and innovative manufacturing technologies. The CGMP initiative was spurred by the fact that since 1978, when the last major revision of the CGMP regulations was published, there have been many advances in manufacturing technologies and in our understanding of quality systems. Many pharmaceutical manufacturers are implementing comprehensive, modern quality systems and risk management approaches. The Agency also saw a need to address the harmonization of the CGMPs and other non-U.S. pharmaceutical regulatory systems as well as FDA’s own medical device quality systems regulations.

The CGMP initiative steering committee created a Quality System Guidance Development working group (QS working group) to compare the current CGMP regulations, which call for specific quality management elements, to other existing quality management systems. The QS working group mapped the relationship between CGMP regulations (parts 210 and 211 and the

1978 Preamble to the CGMP regulations[2]) and various quality system models, such as the Drug Manufacturing Inspections Program (i.e., systems-based inspectional program),[3] the Environmental Protection Agency's Guidance for Developing Quality Systems for Environmental Programs, ISO Quality Standards, other quality publications, and experience from regulatory cases. The QS working group determined that, although the regulations do provide great flexibility, the CGMP regulations do not consider all of the elements that today constitute most quality management systems. The CGMP regulations and other systems differ somewhat in organization and in certain constituent elements; however, they are very similar and share underlying principles. For example, the CGMP regulations stress quality control. More recently developed quality systems stress quality management, quality assurance, and the use of risk management tools, in addition to quality control. The QS working group decided that it would be very useful to examine exactly how the CGMP regulations and the elements of a modern, comprehensive quality system fit together in today's manufacturing world. This guidance is the result of that examination.

B. Goal of the Guidance

This guidance describes a comprehensive quality systems model, which, if implemented, will allow manufacturers to operate robust, modern quality systems that are fully compliant with CGMP regulations. The guidance demonstrates how and where the requirements of the CGMP regulations fit within this comprehensive model. The inherent flexibility of the CGMP regulations should enable manufacturers to implement a quality system in a form that is appropriate for their specific operations.

The overarching philosophy articulated in both the CGMP regulations *and* in robust modern quality systems is:

Quality should be built into the product, and testing alone cannot be relied on to ensure product quality.

This guidance is intended to serve as a bridge between the 1978 regulations and our current understanding of quality systems. In addition to being part of the FDA's CGMP initiative, this guidance is being issued for a number of reasons:

- A quality system addresses the public and private sectors' mutual goal of providing a high-quality drug product to patients and prescribers. A well-built quality system should prevent or reduce the number of recalls, returned or salvaged products, and defective products entering the marketplace.
- It is important that we harmonize the CGMPs to the extent possible with other widely used qu management systems including ISO 9000, non-U.S. pharmaceutical quality management requirements, and FDA's own medical device quality system regulations. With the globalizati of pharmaceutical manufacturing and the increasing prevalence of drug- and biologic-device combination products, the convergence of quality management principles across different regi and among various product types is very desirable.
- The FDA has concluded that modern quality systems, when coupled with manufacturing proc and product knowledge, can handle many types of changes to facilities, equipment, and proces without the need for a regulatory submission. Manufacturers with appropriate process knowle

and a robust quality system should be able to implement many types of improvements without the need for a prior regulatory filing. In addition, an effective quality system, by lowering the risk manufacturing problems, may result in shorter and fewer FDA inspections.

- A quality system can provide the necessary framework for implementing *quality by design*[4] (building in quality from the development phase and throughout a product's life-cycle), continuous improvement, and risk management in the drug manufacturing process. A quality system adopted by a manufacturer can be tailored to fit the specific environment, taking into account factors such as scope of operations, complexity of processes, and appropriate use of fi resources.

C. Scope of the Guidance

This guidance applies to manufacturers of drug products (finished pharmaceuticals), including products regulated by the Center for Biologics Evaluation and Research (CBER), the Center for Drug Evaluation and Research (CDER), and the Center for Veterinary Medicine (CVM). It may also be useful to manufacturers of components used in the manufacture of these products.

This document is ***not*** intended to create new expectations for pharmaceutical manufacturing that go beyond the requirements laid out in the current regulations nor is the guidance intended to be a guide for the conduct of FDA inspections. Rather, the document explains how implementing comprehensive quality systems can help manufacturers achieve compliance with 21 CFR parts 210 and 211. Although the QS working group found that many of the quality system elements correlate with specific CGMP requirements, some do not. In the end, the Agency expects compliance with the CGMP regulations, and FDA's inspection program remains geared to compliance with those regulations.

D. Organization of this Draft Guidance

To provide a reference familiar to industry, the quality systems model described in this guidance is organized — in its major sections — according to the structure of international quality standards. Major sections of the model include the following:

- Management Responsibilities
- Resources
- Manufacturing Operations
- Evaluation Activities

Under each of these sections the key elements found in modern quality systems are discussed. When an element correlates with a CGMP regulatory requirement, we note that correlation. In some cases, a specific CGMP regulation is discussed in more detail as it relates to a quality system element. At the end of each section, a table is included listing the quality system elements of that section and the specific CGMP regulations with which they correlate. A glossary is included at the end of the document.

III. CGMPS AND THE CONCEPTS OF MODERN QUALITY SYSTEMS

Several key concepts are critical for any discussion of modern quality systems. The following concepts are used throughout this guidance as they relate to the manufacture of pharmaceutical products.

A. Quality

Every pharmaceutical product has established identity, strength, purity, and other quality characteristics designed to ensure the required levels of safety and effectiveness. For the purposes of this draft guidance document, the phrase *achieving quality* means achieving these characteristics for the product.

B. Quality by Design and Product Development

Quality by design means designing and developing manufacturing processes *during the product development* stage to consistently ensure a predefined quality at the end of the manufacturing process.[5] A quality system provides a sound framework for the transfer of process knowledge from development to the commercial manufacturing processes and for postdevelopment changes and optimization

C. Risk Management and Risk Assessment

The concept *risk management* is a major focus of the Pharmaceutical CGMPs for the 21st Century Initiative. Risk management can guide the setting of specifications and process parameters. Risk assessment is also used in determining the need for discrepancy investigations and corrective action. As risk assessment[6] is used more formally by manufacturers, it can be implemented within the quality system framework.

D. CAPA (Corrective and Preventive Action)

CAPA is a well-known CGMP regulatory concept that focuses on investigating and correcting discrepancies and attempting to prevent recurrence. Quality system models discuss CAPA as three concepts, all of which are used in this guidance.

- Remedial corrections
- Root cause analysis with corrective action to prevent recurrence
- Preventive action to prevent initial occurrence

E. Change Control

Change control is another well-known CGMP regulatory concept that focuses on managing change to prevent unintended consequences. The major implementation of change control in the CGMP regulations is through the assigned responsibilities of the quality control unit. Certain manufacturing changes (e.g., changes that alter specifications, a critical product attribute or bioavailability) require regulatory filings and prior regulatory approval (601.12 and 314.70).

A quality system also contains change control activities, including quality planning and control of revisions to specifications, process parameters, and procedures. In this guidance, *change* is discussed in terms of creating a regulatory environment that encourages change towards continuous improvement. This means a manufacturer is empowered to make changes based on the variability of materials used in manufacturing and optimization of the process from learning over time.

F. The Quality Unit

Many of the modern quality systems ideas described in this section correlate very closely with the CGMP regulations (refer to the charts later in the document). Current industry practice generally divides the responsibilities of the Quality Control Unit (QCU), as defined in the CGMP regulations, between quality control (QC) and quality assurance (QA) functions.

- QC usually consists of testing of selected in-process materials and finished products to evaluate the performance of the manufacturing process, and to ensure adherence to proper specifications and limits.
- QA primarily includes the review and approval of all procedures related to production, maintenance, and review of associated records, and auditing, and performing trend analyses.

This guidance uses the term *quality unit*[7] (QU) to reflect modern practice while remaining consistent with the CGMP definition in 21 CFR 210.3(b)(15). The concept *quality unit* is also consistent with modern quality systems in ensuring that the various operations associated with all systems are appropriately conducted, approved, and monitored. The CGMP regulations specifically assign the quality unit the authority to create, monitor, and implement the quality system. However, the quality unit is not meant to take on the responsibilities of other units of a manufacturer's organization, such as the responsibilities handled by manufacturing personnel, engineers, and development scientists.[8]

Other CGMP assigned responsibilities of the quality unit are consistent with a modern quality system approaches (see § 211.22):

- Ensuring that controls are implemented and completed satisfactorily during manufacturing operations
- Ensuring that developed procedures and specifications are appropriate and followed, including those used by a firm under contract to the manufacturer
- Approving or rejecting in-process materials and drug products — although such activities do not substitute for, or preclude, the daily responsibility of manufacturing personnel to build quality into the product
- Reviewing production records and investigating any unexplained discrepancies

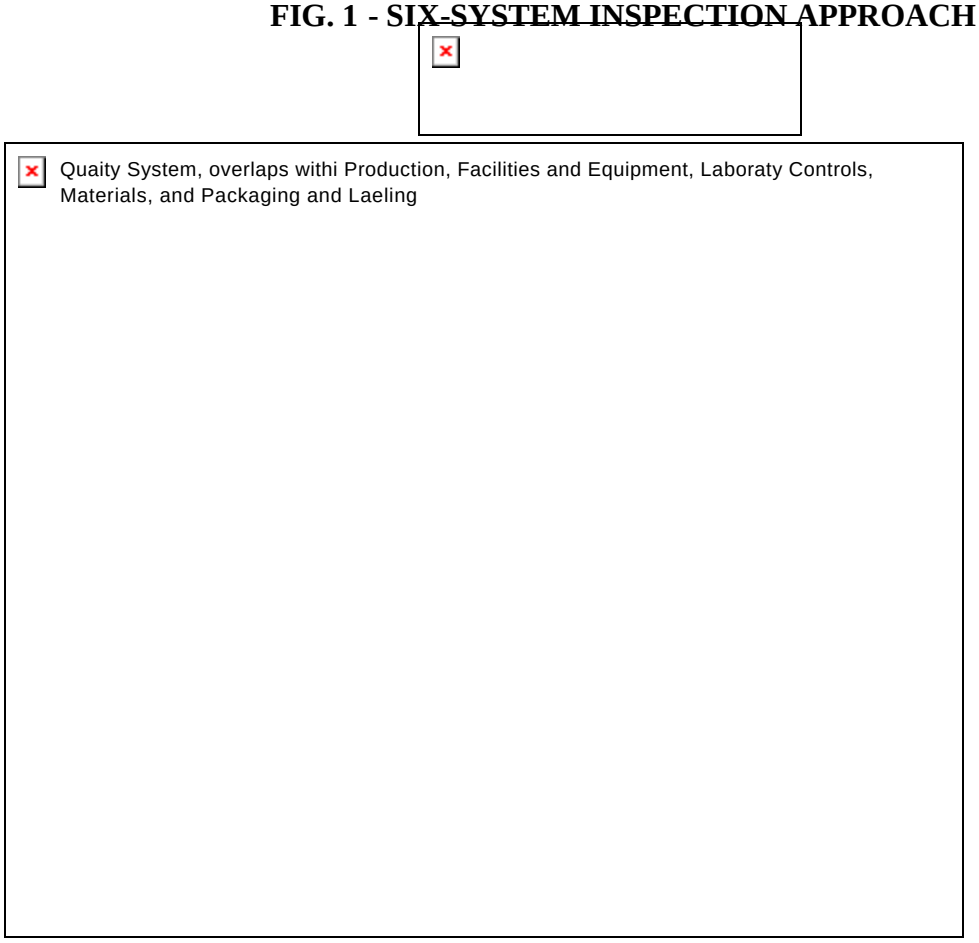
Under a robust quality system, the manufacturing units and the quality unit can remain independent, but still be included in the total concept of producing quality products. In very small operations, a single individual can function as the quality unit. That person is still accountable for implementing all the controls and reviewing results of manufacture to ensure that product quality standards have been met.

G. Six-system Inspection Model

The FDA's Drug Manufacturing Inspection Compliance Program, which constitutes instructions to FDA personnel for conducting inspections, is a systems-based approach for inspections and is very consistent with the robust quality systems model presented in this guidance.[9] The diagram below shows the relationship among the six systems: the quality system and the five manufacturing systems. The quality system provides the foundation for the manufacturing systems that are linked and function within it. The quality systems model described in this guidance does not treat the five manufacturing systems as discrete entities, but instead integrates them into appropriate sections of the model. Those familiar with the six-system inspection

approach will see organizational differences in this guidance; however, the inter-relationship should be readily apparent. One of the important themes of the systems based inspection compliance program is to be able to assess whether each of the systems is in a state of control. The quality system model presented in this guidance will also serve to help firms achieve the desired state of control.

FIG. 1 - SIX-SYSTEM INSPECTION APPROACH



IV. THE QUALITY SYSTEMS MODEL

The goal of this section is to describe a model for use in pharmaceutical manufacturing that can help achieve compliance with CGMP regulations. It should be noted that implementing an effective quality system in a manufacturing organization will require significant costs in time and resources. However, the long-term benefits of implementing a quality system will outweigh the costs.[10]

This section describes a robust quality systems model, which, if implemented, can provide the controls needed to consistently produce a product of acceptable quality. Where applicable, the relationship between elements of this model and CGMP regulations is noted. At the end of each section, a table shows how the specific CGMP regulations correlate to the elements in the quality systems model. As already explained, many of the quality systems elements correlate closely with the CGMP regulations. It is important to emphasize that this guidance is not recommending new regulatory requirements. The guidance is intended to provide recommendations to manufacturers who are implementing, or plan to implement, a quality systems model to help them comply with CGMP regulations. FDA regulatory and inspectional coverage will remain focused on the specific CGMP regulations.

The model is organized into four major sections:

- Management Responsibilities
- Resources
- Manufacturing Operations
- Evaluation Activities

Under each of these sections, the specific elements of a robust modern quality systems model are described. When elements of the quality systems model correlate with specific CGMP regulations, this correlation is noted.

A. Management Responsibilities

Modern robust quality systems models call for management to play a key role in the design, implementation, and management of the quality system. For example, management is responsible for establishing the quality systems structure appropriate for the specific organization. Management has ultimate responsibility to provide the leadership needed for the successful functioning of the quality system. This section describes management's role in developing, implementing, and managing a robust quality system. There is little overlap with the CGMP regulations in this section (see the table at the end of the section).

1. Provide Leadership

In a robust, modern quality system, senior management demonstrates commitment to developing and maintaining their quality system. Leadership is demonstrated by aligning quality system plans with the manufacturer’s strategic plans to ensure that the quality system supports the manufacturer’s mission and strategies. Senior managers set implementation priorities and develop action plans. Managers can provide support of the quality system by:

- Actively participating in system design, implementation, and monitoring, including

system review (see IV.A.5.)

- Advocating continual improvement of operations and the quality system
- Committing necessary resources

In a robust quality systems environment, managers should demonstrate strong and visible support for the quality system and ensure its global implementation throughout the organization (e.g., across multiple sites).

Managers should also encourage internal communication on quality issues at all levels in the organization. Communication should be ongoing among research and development, regulatory affairs, manufacturing, and quality unit personnel on issues that affect quality, with management included whenever appropriate.

2. Structure the Organization

When designing a robust quality system, management has the responsibility to determine the structure of the organization and ensure that assigned authorities and responsibilities support the production, quality, and management activities needed to produce quality products. Senior managers have the responsibility to ensure that the organization's structure is documented.

Managers have the responsibility to communicate employee roles, responsibilities, and authorities within the system and ensure that interactions are defined and understood.

An organization also has the responsibility to give the individual who is appointed to manage the quality system the authority to detect problems and effect solutions. Usually, a senior manager administers the quality system and can, thus, ensure that the organization receives prompt feedback on quality issues.

3. Build Your Quality System to Meet Requirements

Implementing a robust quality system can help ensure compliance with regulations related to safety, identity, strength, quality, and purity as long as the quality system addresses the minimum requirements of CGMP regulations as well as the needs of the manufacturer. Under the quality systems model, the Agency recommends that senior managers ensure that the quality system they design and implement provides clear organizational guidance and facilitates systematic evaluation of issues. For example, according to the model, when documenting a quality system, the following should be included.

- The scope of the quality system, including any outsourcing (see IV.B.4.)
- The standard of quality that will be used
- The manufacturer's policies to implement the quality systems criteria, and the supporting objectives (see IV.A.4.)
- The procedures needed to establish and maintain the quality system

It is recommended under a modern quality systems approach that a formal process be established to submit change requests to directives. It is also recommended that, when operating under a quality system, manufacturers develop and document record control procedures to complete,

secure, protect, and archive records, including data, which act as evidence of operational and quality system activities. This approach is consistent with the CGMP regulations, which require manufacturers to develop and document controls for specifications, plans, and procedures that direct operational and quality system activities and to ensure that these directives are accurate, appropriately reviewed and approved, and available for use (see the CGMPs at §§ 211.22 (c) and (d)).

4. Establish Policies, Objectives, and Plans

Under a modern quality system, policies, objectives, and plans provide the means by which senior managers articulate their vision of quality to all levels of the organization.

It is expected that under a quality system senior management would incorporate a strong commitment to quality into the organizational mission. Senior managers are expected to develop an organizational quality policy that aligns with this mission; commit to meeting requirements and improving the quality system; and propose objectives to fulfill the quality policy. Under a quality system, to make the policy relevant, it must be communicated to, and understood by, personnel and contractors (as applicable), and revised as needed.

Managers operating within a quality system are expected to define the quality objectives needed to implement the quality policy. Senior management is expected to ensure that the quality objectives are created at the top level of the organization (and other levels as needed) through a formal quality planning process. Objectives are typically aligned with the manufacturer's strategic plans. A quality system seeks to ensure that managers support the objectives with necessary resources and have measurable goals that are monitored regularly.

Under a quality system, managers would be expected to use quality planning to identify resources and define methods to achieve the quality objectives. It is recommended that quality plans be documented and communicated to personnel to ensure awareness of how their operational activities are aligned with strategic and quality goals.

5. Review the System

System review is a key component in any robust quality system to ensure its continuing suitability, adequacy, and effectiveness. Under a quality system, senior managers are expected to conduct reviews of the whole quality system according to a planned schedule. Such a review typically includes both an assessment of the product as well as customer needs (in this section, *customer* is defined as the recipient of the product and the product is the goods or services being provided). Under a quality system, the review should consider at least the following:

- The appropriateness of the quality policy and objectives
- The results of audits and other assessments
- Customer feedback, including complaints
- The analysis of data trending results
- The status of actions to prevent a potential problem or a recurrence
- Any follow-up actions from previous management reviews
- Any changes in business practices or environment that may affect the quality system (such as the volume or type of operations)

- Product characteristics meet the customer's needs

When developing and implementing new quality systems, reviews should take place more frequently than when the system has matured. Outside of scheduled reviews, the quality system is typically included as a standing agenda item in general management meetings.

Review outcomes typically include:

- Improvements to the quality system and related quality processes
- Improvements to manufacturing processes and products
- Realignment of resources

Under a quality system, the results of a management review are expected to be recorded. Planned actions should be implemented using effective corrective and preventive action and change control procedures.

The following table shows how the CGMP regulations correlate to specific elements in the quality systems model for this section. Manufacturers should always refer to the specific regulations to ensure that they are complying with all regulations.

21 CFR CGMP Regulations Related to Management Responsibilities	
Quality System Element	**Regulatory Citations**
1. Leadership	—
2. Structure	Establish quality function: § 211.22 (a) (see definition § 210.3(b)(15))
	Notification: § 211.180(f)
3. Build QS	QU procedures: § 211.22(d)
	QU procedures, specifications: § 211.22(c), with reinforcement in: §§ 211.100(a), 211.160(a)
	QU control steps: § 211.22(a), with reinforcement in §§: 211.42 (c), 211.84(a), 211.87, 211.101(c)(1), 211.110(c), 211.115 (b), 211.142, 211.165(d), 211.192
	QU quality assurance; review/investigate: § 211.22(a), 211.100 (a-b) 211.180(f), 211.192, 211.198(a)
	Record control: § 211.180(a-d), 211.180(c), 211.180(d), 211.180(e), 211.186, 211.192, 211.194, 211.198(b)

4. Establish Policies, Objectives and Plans	Procedures: § 211.22(c-d), 211.100(a)
5. System Review	Record review: § 211.180(e), 211.192, 211.198(b)(2)

B. Resources

Appropriate allocation of resources is key to creating a robust quality system and to complying with the CGMP regulations. This section discusses the role of resources in developing, implementing, and managing a robust quality system that fully complies with the CGMP regulations.

1. General Arrangements

Under a robust quality system, there should be sufficient allocation of resources for quality system and operational activities. Under the model, senior management, or a designee, is responsible for providing adequate resources for the following:

- To supply and maintain the appropriate facilities and equipment to consistently manufacture a quality product
- To acquire and receive materials that are suitable for their intended purpose
- For processing the materials to produce the finished drug product
- For laboratory analysis of the finished drug product, including collection, storage, and examination of in-process, stability, and reserve samples

2. Develop Personnel

Under a quality system, senior management is expected to support a problem-solving and communicative organizational culture. Managers are expected to encourage communication by creating an environment that values employee suggestions and acts on suggestions for improvement. Management is also expected to develop cross-cutting groups to share ideas to improve procedures and processes.

In the quality system, it is recommended that personnel be qualified to do the operations that are assigned to them in accordance with the nature of, and potential risk to quality presented by, their operational activities. Under a quality system, managers are expected to define appropriate qualifications for each position to help ensure individuals are assigned appropriate responsibilities. Personnel should also understand the impact of their activities on the product and the customer (this quality systems parameter is also found in the CGMP regulations, which identify specific qualifications (i.e., education, training, and experience or any combination thereof; see §§ 211.25(a) & (b)).

Under a quality system, continued training is critical to ensure that the employees remain proficient in their operational functions and in their understanding of CGMP regulations. Typical quality systems training would address the policies, processes, procedures, and written

instructions related to operational activities, the product/service, the quality system, and the desired work culture (e.g., team building, communication, change, behavior). Under a quality system (and the CGMP regulations), training is expected to focus on both the employees' specific job functions and the related CGMP regulatory requirements.

Under a quality system, managers are expected to establish training programs that include the following:

- Evaluation of training needs
- Provision of training to satisfy these needs
- Evaluation of effectiveness of training
- Documentation of training and/or re-training

When operating in a robust quality system environment, it is important that supervisory managers ensure that skills gained from training be incorporated into day-to-day performance.

3. Facilities and Equipment

Under a quality system, the technical experts (e.g., engineers, development scientists), who have an understanding of pharmaceutical science, risk factors, and manufacturing processes related to the product, are responsible for specific facility and equipment requirements.

According to CGMP regulations, the QCU has the responsibility of reviewing and approving all initial design criteria and procedures pertaining to facilities and equipment and any subsequent changes (see § 211.22(c)). FDA can, as resources permit, provide a preoperational review of manufacturing facilities.[11]

According to the CGMP regulations, equipment must be qualified, calibrated, cleaned, and maintained to prevent contamination and mix-ups (§§ 211.63, 211.67, 211.68). Note that the CGMP regulations require a higher standard for calibration and maintenance than most generic quality system models. The CGMP regulations place as much emphasis on process equipment as on testing equipment (§ 211.42(b)), while most quality systems focus only on testing equipment. [12]

4. Control Outsourced Operations

When outsourcing, a second party is hired under a contract to perform the operational processes that are part of a manufacturer's inherent responsibilities. For example, a manufacturer may hire another firm to package and label or perform CGMP regulation training. Quality systems call for contracts (quality agreements) that clearly describe the materials or service, quality specifications responsibilities, and communication mechanisms.

Under a quality system, the manufacturer ensures that the contract firm is qualified. The firm's personnel should be adequately trained and monitored for performance according to their quality system, and the contract firm's and contracting manufacturer's quality standards should not conflict. It is critical in a quality system to ensure that the contracting manufacturer's officers are familiar with the specifics requirements of the contract. However, under the CGMP requirements, the QCU is responsible for approving or rejecting products or services provided

under contract (see § 211.22(a)).

As the following table illustrates, the CGMP regulations are consistent with the elements of a quality system in many areas in this section. However, manufacturers should always refer to the specific regulations to ensure that they are complying with all regulations.

21 CFR CGMP Regulations Related to Resources	
Quality System Element	**Regulatory Citation**
1. General Arrangements	—
2. Develop Personnel	Qualifications: § 211.25(a)
	Staff number: § 211.25(c)
	Staff training: § 211.25(a-b)
3. Facilities and Equipment	Buildings and facilities: §§ 211.22(b), 211.28(c), 211.42 – 211.58, 211.173
	Equipment: § 211.63 – 211.72, 211.105, 211.160(b)(4), 211.182
	Lab facilities: § 211.22(b)
4. Control Outsourced Operations	Consultants: § 211.34
	Outsourcing: § 211.22(a)

C. Manufacturing Operations

There is significant overlap between the elements of a quality system and the CGMP regulation requirements for manufacturing operations. It is important to emphasize again that FDA's enforcement programs and inspectional coverage remain based on the CGMP regulations. When quality system elements in this section do not correlate to the CGMP regulations, the guidance makes recommendations to help facilitate compliance with the CGMP regulations. The language in this section has been tailored to the pharmaceutical manufacturing environment.

1. Design and Develop Product and Processes

In a modern quality systems manufacturing environment, the significant characteristics of the product being manufactured should be defined, from design to delivery, and control should be exercised over all changes. Quality and manufacturing processes and procedures — and changes to them — should be defined, approved, and controlled (CGMP also requires this; see § 211.100). It is important to establish responsibility for designing or changing products.

Documenting associated processes will ensure that critical variables are identified.

This documentation includes:

- Resources and facilities needed
- Procedures to carry out the process
- Identification of the process owner who will maintain and update the process as needed
- Identification and control of critical variables
- Quality control measures, necessary data collection, monitoring, and appropriate controls for the product and process
- Any validation activities, including operating ranges and acceptance criteria
- Effects on related process, functions, or personnel

As discussed under section IV.A. Management, above, the model calls for managers to ensure that product specifications and process parameters are determined by the appropriate technical experts (e.g., engineers, development scientists). In the pharmaceutical environment, experts would have an understanding of pharmaceutical science, risk factors, and manufacturing processes as well as how variations in materials and processes can ultimately affect the finished product.

2. Monitor Packaging and Labeling Processes

Packaging and labeling controls, critical stages in the pharmaceutical manufacturing process, are not specifically addressed in quality systems models. Therefore, the Agency recommends that manufacturers always refer to the packaging and labeling control regulations at 21 CFR 211 Subpart G. In addition — and this ***is*** consistent with modern quality systems — FDA recommends that, as part of the design process, before commercial production, the controls for all processes within the packaging and labeling system be planned and documented in written procedures. The procedures should outline quality control activities and the responsible positions. Specifications and controls for the packaging and labeling materials should also be determined before commercial production. Distinct labels with discriminating features for different products, such as a product marketed with different strengths, should be included to prevent mislabeling and resulting recalls.

In modern quality systems environments, when new or reengineered processes are developed, it is expected that they will be designed in a controlled manner. A design plan would include authorities and responsibilities; design and development stages; and appropriate review, verification, and validation. If different groups are involved in design and development, the model recommends that responsibilities of the different groups be documented to avoid omission of key duties and ensure that the groups communicate effectively. Plans should be updated when needed during the design process. Prior to implementation of processes (or shipment of a product), a robust quality system will ensure that the process and product will perform as intended. Change controls should be maintained throughout the design process.

3. Examine Inputs

In modern quality systems models, the term *input* refers to any material that goes into a final

product, no matter whether the material is purchased by the manufacturer or produced by the manufacturer for the purpose of processing. *Materials* can include items such as components (e.g., ingredients, process water, and gas), containers, and closures. A robust quality system will ensure that all inputs to the manufacturing process are reliable because quality controls will have been established for the receipt, production, storage, and use of all inputs.

The quality systems model calls for the verification of the components and services provided by suppliers and contractors; however, the model offers a method for implementing verification that is different from those in the CGMP regulations.

The CGMP regulations require either testing or use of a certificate of analysis (COA) plus an identity analysis (see §§ 211.22 and 211.84). In the preamble to the CGMP regulations (see comment 239 in the preamble), these requirements were explicitly interpreted. The preamble states that reliability can be validated by conducting tests or examinations and comparing the results to the supplier's COA. Sufficient initial tests must be done to establish reliability and to determine a schedule for periodic rechecking. As an essential element of purchasing controls, it is recommended that data for acceptance and rejection of materials be analyzed for information on supplier performance.[13]

The quality systems approach also calls for the auditing of suppliers on a periodic basis. During the audit, the manufacturer can observe the testing or examinations conducted by the supplier to help determine the reliability of the supplier's COA. An audit should also include a systematic examination of the supplier's quality system to ensure that reliability is maintained. The FDA recommends that a combination approach be used (i.e., verifying the suppliers' COA through analysis and audits of the supplier). If full analytical testing is not done, the audit should cover the supplier's analysis. (A specific identity test is still required in § 211.84(d)(1).)

Under a quality systems approach, there should be procedures to verify that materials are from approved sources (for application and licensed products, certain sources are specified in the submissions). Procedures should also be established to encompass the acceptance, use, or the rejection and disposition of materials produced by the facility (e.g., purified water). Systems that produce these in-house materials should be designed, maintained, qualified, and validated where appropriate to ensure the materials meet their acceptance criteria.

In addition, we recommend that changes to materials (e.g., specification, supplier, or materials handling) be implemented through a change control system (certain changes require review and approval by the quality control unit (see § 211.100(a)). It is also important to have a system in place to respond to changes in materials from suppliers so that necessary adjustments to the process can be made and unintended consequences prevented.

4. Perform and Monitor Operations

The core purpose of implementing a quality systems approach is to enable a manufacturer to more efficiently and effectively perform and monitor operations. The goal of establishing, adhering to, measuring, and documenting specifications and process parameters is to objectively assess whether an operation is meeting its design (and product performance) objectives. In a robust quality system, production and process controls should be designed to ensure that the finished products have the identity, strength, quality and purity they purport or are represented to possess (CGMP also requires this; see § 211.100(a)).

In a modern quality system, a design concept established during product development typically

matures into a commercial design after process experimentation and progressive modification. Areas of process weakness should be identified, and factors that are influential on critical quality attributes should receive increased scrutiny. (The FDA recommends that scale-up studies be used to help demonstrate that a fundamentally sound *design* has been fully realized.) A sufficiently robust manufacturing process should be in place prior to commercial production. With proper design (see section IV.C.1), and reliable mechanisms to transfer process knowledge from development to commercial production, a manufacturer should be able to validate the manufacturing process.[14] In a quality system, process validation provides initial proof, through commercial batch manufacture, that the design of the process produces the intended product quality. Sufficient testing data will provide essential information on performance of the new process, as well as a mechanism for continuous improvement. Modern equipment with the potential for continuous monitoring and control can further enhance this knowledge base. Although initial commercial batches can provide evidence to support the validity and consistency of the process,[15] the *entire life-cycle* should be addressed by the establishment of continuous improvement mechanisms in the quality system.[16] Thus, in accordance with the quality systems approach, process validation is not a one time event, but an activity that continues.

As experience is gained in commercial production, opportunities for process improvements may become evident. (CGMP regulations at § 211.180 require the review and evaluation of records to determine the need for any change. These records contain data and information from production that provide insights into the product's state of control. Change control systems should provide for a dependable mechanism for prompt implementation of technically sound manufacturing improvements.)

Under a quality system, written procedures are followed and deviations from them are justified and documented (CGMP requires this; see § 211.100(b)) to ensure that the manufacturer can trace the history of the product, as appropriate, concerning personnel, materials, equipment, and chronology and that processes for product release are complete and recorded.

Both the CGMP regulations (see § 211.110) and quality systems models call for the monitoring of critical process parameters during production.

- Process steps should be verified using a validated computer system or a second person. Batch production records should be prepared contemporaneously with each phase of production. Although time limits can be established when they are important to the quality of the finished product (CGMP addresses this; see § 211.111), this does not preclude the ability to establish production controls based on in-process parameters that can be based on desired process endpoints measured using real time testing or monitoring apparatus (e.g., blend until mixed vs. blend for 10 minutes).

- Procedures should be in place to prevent objectionable microorganisms in finished product that is not required to be sterile and to prevent microbial contamination of finished products purported to be sterile (CGMP also requires this; see § 211.113) Sterilization processes should be validated (CGMP also requires this; see § 211.113(b)) for sterile drugs.[17]

Pharmaceutical products must meet their specifications and manufacturing processes must consistently meet their parameters. Under a quality system, selected data are used to evaluate the quality of a process or product. In addition, data collection can provide a means to encourage and analyze potential suggestions for improvement. A quality systems approach calls for the

manufacturer to develop procedures that monitor, measure, and analyze the operations (including analytical methods and/or statistical techniques). Knowledge continues to accumulate from development through the entire commercial life of the product. Significant unanticipated variables should be detected by a well-managed quality system and adjustments implemented. Procedures should be revisited as needed to refine operational design based on new knowledge. Process understanding increases with experience and helps identify the need for change towards continuous improvement. When implementing data collection procedures, consider the following:

- Are collection methods documented?
- When in the product life-cycle will the data be collected?
- How and to whom will measurement and monitoring activities be assigned?
- When should analysis and evaluation (e.g. trending) of laboratory data be performed (see V.E.1.)?
- What records are needed?

A modern quality system approach indicates that change control is warranted when data analysis or other information reveals an area needing improvement. Changes to an established process should be controlled and documented to ensure that desired attributes for the finished product will be met (CGMP also requires this; see § 211.100(a)).

Change control with regard to pharmaceuticals is addressed in more detail in the CGMPs. When developing a process change, it is important to keep the process design and scientific knowledge of the product in mind. When major design issues are encountered through process experience, a firm may need to revisit the adequacy of the design of the manufacturing facility (§ 211.42), the design of the manufacturing equipment (§ 211.63), the design of the production and control procedures (§ 211.100), or the design of laboratory controls (§ 211.160). When implementing a change, determining its effect should be based on monitoring and evaluating those specific elements that may be affected based on understanding of the process. This allows the steps taken to implement a change and the effects of the change on the process to be considered systematically. Evaluating the effects of a change can entail additional tests or examinations of subsequent batches (e.g., additional in-process testing or additional stability studies).

The quality system elements identified in this guidance, if implemented, will help a manufacturer manage change and implement continuous improvement in manufacturing.

Under a quality system, procedures should be in place to ensure the accuracy of test results. Test results that are out of specification may be due to testing problems or manufacturing problems and should be investigated.[18] Invalidation of test results should be scientifically and statistically sound and justified.

The Agency recommends that, upon the completion of manufacturing and to maintain quality, the manufacturer should consider shipment requirements to meet special handling needs (in the case of pharmaceuticals, one example might be refrigeration).

Under a quality system, trends should be continually identified and evaluated. One way of accomplishing this is the use of statistical process control. The information from trend analyses can be used to continually monitor quality, identify potential variances before they become problems, bolster data already collected for the annual review, and facilitate improvement

throughout the product life-cycle. Process capability assessment can serve as a basis for determining the need for changes that can result in process improvements and efficiency (see IV.D.1.).

5. Address Nonconformities

A key component in any quality system is handling nonconformities and/or deviations. The investigation, conclusion, and follow-up should be documented (CGMP also requires this; see 21 CFR 211.192). To ensure that a product conforms to requirements and expectations, it is important to measure process and the product attributes (e.g., specified control parameters strength) as planned. Discrepancies may be detected during any stage of the process by an employee or during quality control activities. Not all discrepancies will result in product defects; however, it is important to document and handle them appropriately. A discrepancy investigation process is critical when a discrepancy is found that affects product quality (CGMP also requires this; see § 211.192).

In a quality system, it is critical to develop and document procedures to define responsibilities for halting and resuming operations, recording the nonconformity, investigating the discrepancy, and taking remedial action. The corrected product or process should also be re-examined for conformance and assessed for the significance of the nonconformity (CGMP also requires this; see § 211.115). If the nonconformity is significant, based on consequences to process efficiency, product quality, safety, and availability, it is important to evaluate how to prevent recurrence.

Under a quality system, if a product or process does not meet requirements and has not been released for use, it is essential to identify or segregate it so that it is not distributed to the customer by accident. Remedial action may include correcting the nonconformity; or, with proper authorization, allowing the product to proceed with proper authorization and the problem documented, or using the product for another application; or rejecting the product. If an individual product that does not meet requirements has been released, the product can be recalled. [19] Customer complaints should be handled as discrepancies and be investigated (CGMP addresses this; see § 211.198).

The following table shows how the CGMP regulations correlate to specific elements in the quality systems model. Manufacturers should always refer to the specific regulations to ensure that they are complying with all regulations.

21 CFR CGMP Regulations Related to Manufacturing Operations

Quality System Element	Regulatory Citation
1. Design and Develop Product and Processes	Production: § 211.100(a)
2. Examine Inputs	Materials: §§ 210.3(b), 211.80 – 211.94, 211.101, 211.122, 211.125
3. Perform and Monitor Operations	Production: §§ 211.100, 211.103, 211.110, 211.111, 211.113
	QC criteria: §§ 211.22(a-c), 211.115(b), 211.160(a), 211.165(d)

	QC checkpoints: §§ 211.22 (a), 211.84(a), 211.87, 211.110 (c)
4. Address Nonconformities	Discrepancy investigation: §§ 211.22(a), 211.115, 211.192, 211.198 Recalls: 21 CFR Part 7

D. Evaluation Activities

As in the previous section, the elements of a quality system correlate closely with the requirements in the CGMP regulations. See the table at the end of the section for the specifics.

1. Analyze Data for Trends

Quality systems call for continually monitoring trends and improving systems. This can be achieved by monitoring data and information, identifying and resolving problems, and anticipating and preventing problems.

Quality systems procedures involve collecting data from monitoring, measurement, complaint handling, or other activities, and tracking this data over time, as appropriate. Analysis of data can provide indications that controls are losing effectiveness. The information generated will be essential to achieving problem resolution or problem prevention (see IV.D.3.).

Although the annual review required in the CGMP regulations (§ 211.180(e)) call for review of representative batches on an annual basis; quality systems calls for trending on a regular basis. Trending enables the detection of potential problems as early as possible to plan corrective and preventive actions. Another important concept of modern quality systems is the use of trending to examine processes as a whole; this is consistent with the annual review approach. These trending analyses can help focus internal audits (see IV.D.2.).

2. Conduct Internal Audit

A quality systems approach calls for audits to be conducted at planned intervals to evaluate effective implementation and maintenance of the quality system and to determine if processes and products meet established parameters and specifications. As with other procedures, audit procedures should be developed and documented to ensure that the planned audit schedule takes into account the relative risks of the various quality system activities, the results of previous audits and corrective actions, and the need to audit the entire system at least annually. Quality systems recommend that procedures describe how auditors are trained in objective evidence gathering, their responsibilities, and auditing procedures. Procedures should also define auditing activities such as the scope and methodology of the audit, selection of auditors, and audit conduct (audit plans, opening meetings, interviews, closing meeting and reports). It is critical to maintain records of audit findings and assign responsibility for follow-up to prevent problems from recurring (see IV.D.3.).

The quality systems model calls for managers who are responsible for the areas audited to take timely action to resolve audit findings and ensure that follow-up actions are completed, verified, and recorded. (FDA's policy is to not routinely review or copy reports and records that result from internal audits per Compliance Policy Guide 130.300.[20])

3. Risk Assessment

Effective decision-making in a quality systems environment is based on an informed understanding of quality issues. Elements of risk should be considered relative to intended use, and in the case of pharmaceuticals, patient safety and ensuring availability of medically necessary drug products. Management should assign priorities to activities or actions based on the consequences of action or inaction — otherwise known as *risk assessment*. It is important to engage appropriate parties in assessing the consequences. Such parties include customers, appropriate manufacturing personnel, and other stakeholders. Assessing consequences includes using the manufacturer's risk assessment model to address risks, developing a strategy by deciding which options to implement, taking actions to implement the strategy, and evaluating the results. Since risk assessment is a reiterative process, the assessment should be repeated if new information is developed that changes the need for, or nature of, risk management.

In a manufacturing quality systems environment, risk assessment is used as a tool in the development of product specifications and critical process parameters. Used in conjunction with process understanding, risk assessment helps manage and control change.

4. Corrective Action

Corrective action is a reactive tool for system improvement to ensure that significant problems do not recur. Both quality systems and the CGMP regulations emphasize corrective actions. Quality systems approaches call for procedures to be developed and documented to ensure that the need for action is evaluated relevant to the possible consequences, the root cause of the problem is investigated, possible actions are determined, a selected action is taken within a defined timeframe, and the effectiveness of the action taken is evaluated. It is essential to maintain records of corrective actions taken (CGMP also requires this; see § 211.192).

It is essential to determine what actions are needed to prevent problem recurrence using information from sources such as:

- Nonconformance reports and rejections
- Complaints
- Internal and external audits
- Data and risk analyses related to operations and quality system processes
- Management review decisions

5. Preventive Action

Being proactive is an essential tool in quality systems management. Tasks can include

succession planning, training, capturing institutional knowledge, and planning for personnel, policy, and process changes.

A preventive action procedure will help ensure that potential problems and root causes are identified, possible consequences assessed, and actions considered. The selected preventative action should be evaluated and recorded, and the system should be monitored for the effectiveness of the action. Problems can be anticipated and their occurrence prevented using information from reviews of data and risk analyses associated with operational and quality system processes, and by keeping abreast of changes in scientific and regulatory requirements.

6. Promote Improvement

The effectiveness and efficiency of the quality system can be improved through the quality activities described in this guidance. Management may choose to use other improvement activities as appropriate. It is critical that senior management be involved in the evaluation of this improvement process (section IV.D.3.).

The following table shows how the CGMP regulations correlate to specific elements in the quality systems model for this section. Manufacturers should always refer to the specific regulations to ensure that they are complying with all regulations.

21 CFR CGMP Regulations Related to Evaluation Activities	
Quality System Element	**Regulatory Citation**
1. Analyze Data for Trends	Annual Review: § 211.180(e)
2. Conduct Internal Audits	Annual Review: § 211.180(e)
3. Risk Assessment	—
4. Corrective Action	Discrepancy investigation: § 211.22(a), 211.192
5. Preventive Action	—
6. Promote Improvement	—

V. CONCLUSION

Implementation of a *comprehensive quality systems model for* human and veterinary pharmaceutical products, including biological products, will facilitate compliance with 21 CFR parts 210 and 211. The central goal of a quality system is to ensure consistent production of safe and effective products and that these activities are sustainable. Quality professionals are aware that good intentions alone will not ensure good products. A robust quality system will promote process consistency by integrating effective knowledge-building mechanisms into daily

operational decisions. Specifically, successful quality systems share the following characteristics, each of which have been discussed in detail above:

- Science-based approaches
- Decisions based on an understanding of the intended use of a product
- Proper identification and control of areas of potential process weakness
- Responsive deviation and investigation systems that lead to timely remediation
- Sound methods for assessing risk
- Well-defined processes and products, starting from development and extending throughout the product life cycle
- Systems for careful analyses of product quality
- Supportive management (philosophically and financially)

Both good manufacturing practice and good business practice require a robust quality system. When fully developed and effectively managed, a quality system will lead to consistent, predictable processes that ensure that pharmaceuticals are safe, effective, and available for the consumer.

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GLOSSARY

To gain a common understanding of a quality system as a whole, the following terms are used throughout the guidance.

Annual Review - An evaluation, conducted at least annually, which assesses the quality standards of each drug product to determine the need for changes in drug product specifications or manufacturing or control procedures.

CAPA – "Corrective and preventive action": A systematic approach which includes actions needed to: correct ("correction"); prevent recurrence ("corrective action"); and eliminate the cause of potential ("preventive action") nonconforming product and other quality problems. [21CFR 820.100]

Continuous Improvement – ongoing activities to evaluate and positively change products, processes, and the quality system to increase effectiveness.

Correction - Repair, rework, or adjustment and relates to the disposition of an existing discrepancy

Corrective Action - Action taken to eliminate the causes of an existing non-conformity, defect or other undesirable situation to prevent recurrence.

Customer – a person or organization (internal or external) that receives a product or service anywhere along the product's life-cycle.

Discrepancy - Datum or result outside of the expected range, an unfulfilled requirement; may be called non-conformity, defect, deviation, out-of-specification, out-of-limit, out-of-trend, etc.

Metrics - measurements taken over time that monitor, assess, and communicate vital information about the results of a process or activity. Metrics are generally quantitative, but can be qualitative.

Nonconformity – a deficiency in a characteristic, product specification, process parameter, record, or procedure that renders the quality of a product unacceptable, indeterminate or not according to specified requirements.

Packaging Materials – as used in the Packaging and Labeling System, excludes container and closures which are covered by 21 CFR 211 Subpart E (preamble comment # 312).

Pre-production – drug development phase prior to pilot production.

Preventive Action - Action taken to eliminate the cause of a potential non-conformity, defect, or other undesirable situation to prevent occurrence

Product/Service – the intended results of activities or processes; products/services can be tangible or intangible.

Quality – a measure of a product's or service's ability to satisfy the customer's stated or implied

needs.

Quality Assurance – proactive and retrospective activities that provide confidence that requirements are fulfilled.

Quality Control – the steps taken during the generation of a product or service to ensure that it meets requirements and that the product or service is reproducible.

Quality Management – accountability for the successful implementation of the quality system.

Quality Objectives – specific measurable activities or processes to meet the intentions and directions as defined in the quality policy.

Quality Plan – the documented result of quality planning that is disseminated to all relevant levels of the organization.

Quality Planning – a management activity that sets quality objectives and defines the operational and/or quality system processes and the resources needed to fulfill the objectives.

Quality Policy – a statement of intentions and direction issued by the highest level of the organization related to satisfying customers' needs. It is similar to a strategic direction that communicates quality expectations that the organization is striving to achieve.

Quality System – formalized business practices that define management responsibilities for organizational structure, processes, procedures and resources needed to fulfill product/service requirements, customer satisfaction, and continual improvement. In the CGMP regulatory context, the quality system establishes the foundation to promote the effective functioning of the five other major systems.

Quality Unit – A group organized within an organization to promote quality in general practice.

Risk Assessment - A systematic evaluation of the risk of a process by determining what can go wrong (risk identification), how likely is it to occur (risk estimation), and what the consequences are.

Senior Management – top management officials in a firm who have the authority and responsibility to mobilize resources

Stakeholders – an individual or organization having an ownership or interest in the delivery, results and metrics of the quality system framework or business process improvements.

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[1] This draft guidance was developed by the Office of Compliance in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER), the Center for Veterinary Medicine (CVM) and the Office of Regulatory Affairs (ORA).

[2] See Reference #1.

[3] See Reference #2.

[4] This concept is being developed under the ICH Q8 Pharmaceutical Development Expert Working Group.

[5] These concepts are being developed under the ICH-Q8 Pharmaceutical Development Expert Working Group.

[6] This concept is being developed under the ICH Q9 Risk Analysis Expert Working Group.

[7] Generally, the term *quality* unit is used in this guidance. However, *quality control unit* is used when directly quoting parts 210 and 211.

[8] See Reference #1, comment 91.

[9] See Reference #2; This inspectional approach is currently in use by CDER and CBER for blood and blood product inspections. CBER and CVM are developing a similar approach for drug product inspections.

[10] See Reference #3

[11] See Reference #4.

[12] See Reference #5.

[13] The Agency recommends that manufacturers have a measure of the variability of materials that could affect their process controls. For example, certain changes in physical properties may affect the process, which may affect a finished product's dissolution characteristics.

[14] See Reference #6.

[15] Even with good design and development work, initial *conformance batches* only provide confidence that future batches will meet specifications if the process is repeated within defined operating parameters, equipment tolerances, personnel practices, environmental attributes, and material quality.

[16] See Reference #7.

[17] See Reference #8

[18] See Reference #9

[19] See 21 CFR Part 7

[20] See Reference #10.

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