Considerations for Complying With 21 CFR 211.110

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Brittany Avaritt at 240-402-5982 or brittany.avaritt@fda.hhs.gov; (CBER) Office of Communication, Outreach and Development at 800-835-4709 or 240-402-8010; or (CVM) at AskCVM@fda.hhs.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Veterinary Medicine (CVM)

January 2025
Pharmaceutical Quality/Manufacturing Standards (CGMP)

Considerations for Complying With 21 CFR 211.110

Guidance for Industry

Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs
and/or
Office of Communication, Outreach and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010
Email: ocod@fda.hhs.gov
https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances
and/or
Policy and Regulations Staff, HFV-6
Center for Veterinary Medicine
Food and Drug Administration
7500 Standish Place, Rockville, MD 20855
https://www.fda.gov/animal-veterinary/guidance-regulations/guidance-industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Veterinary Medicine (CVM)

January 2025
Pharmaceutical Quality/Manufacturing Standards (CGMP)

TABLE OF CONTENTS

Considerations for Complying With 21 CFR 211.110 Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance, when finalized, will describe considerations for complying with the requirements in 21 CFR 211.110 to ensure batch uniformity and drug product integrity. In addition, this guidance discusses related quality considerations for drug products that are manufactured using advanced manufacturing. It also discusses how manufacturers can incorporate process models into commercial manufacturing control strategies.[2,3]

This guidance applies to the manufacture of human drug products, including biological products, and animal drug products; these will be collectively referred to as drug products in this guidance. This guidance does not apply to the manufacture of active ingredients.

In general, FDA's guidance documents 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

[1] This guidance has been prepared by the Office of Pharmaceutical Quality in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research, the Center for Veterinary Medicine, and the Office of Regulatory Affairs at the Food and Drug Administration.

[2] Process models can be used at any stage of a drug product's life cycle, from development to commercial manufacturing. However, this guidance applies to process models that are used as part of a control strategy during commercial manufacturing. This guidance does not apply to process models used in other phases of the drug product life cycle, such as drug development or technology transfer.

[3] See ICH guidances for industry *Q8(R2) Pharmaceutical Development* (November 2009), *Q9(R1) Quality Risk Management* (May 2023), and *Q10 Pharmaceutical Quality Systems* (April 2009). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

To ensure batch uniformity and drug product integrity, the current good manufacturing practice (CGMP) regulations[4] require, among other things, that manufacturing processes are designed and controlled to ensure that in-process materials consistently and reliably meet predetermined quality requirements.[5] This guidance explains the requirements for drug product manufacturing in § 211.110. This guidance also describes considerations for the use of advanced manufacturing (e.g., 3D printing, continuous manufacturing)[6] and the use of process models as a part of commercial manufacturing control strategies. FDA supports the adoption of advanced manufacturing as a foundation for improving the overall quality and availability of drug products for patients.

Advanced manufacturing is a term for an innovative pharmaceutical manufacturing technology or approach that has the potential to improve the reliability and robustness of the manufacturing process and supply chain and increase timely access to quality medicines for the American public. Advanced manufacturing can integrate novel technological approaches, use established techniques in an innovative way, or apply production methods in a new domain where there may be limited experience or no defined best practices. Advanced manufacturing can potentially be used for new or currently marketed large or small molecule drugs.[7]

All manufacturers, regardless of whether they are using advanced manufacturing, should apply a scientific- and risk-based approach to controlling processes and ensuring drug product quality. This approach should be based on robust product and process understanding. Manufacturers must maintain the process in a state of control over the life of the process to ensure drug product quality, even as materials, equipment, production environment, personnel, and manufacturing procedures change.[8] Planning and executing a system that monitors process performance and drug product quality helps ensure that a state of control is maintained. An effective monitoring system helps maintain a state of control in multiple ways, which include helping manufacturers: (1) ensure that processes and controls are continuously capable of producing a drug product of desired quality; and (2) identify areas for continual improvement.[9] In addition, § 211.110(a) requires that manufacturers establish and follow written procedures "that describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch." Section 211.110(c) also requires that in-process materials are "tested for identity, strength, quality, and purity as appropriate, and approved or rejected by the quality

[4] See 21 CFR parts 210 and 211.

[5] See § 211.110.

[6] Continuous manufacturing can be applied to some or all unit operations in a manufacturing process. This includes the approach in which active ingredient and drug product unit operations are integrated to form a single continuous manufacturing process. Manufacturers who use continuous manufacturing processes must still define batches to be tested for release under 21 CFR 211.165 and for other CGMP requirements, including the requirements in § 211.110 that ensure batch uniformity and drug product integrity. See also 21 CFR 210.3(b)(2) and the ICH guidance for industry *Q13 Continuous Manufacturing of Drug Substances and Drug Products* (March 2023).

[7] CDER established the Framework for Regulatory Advanced Manufacturing Evaluation (FRAME) initiative to prepare a regulatory framework to support the adoption of advanced manufacturing technologies that could bring benefits to patients. This guidance is being issued as part of the FRAME initiative. For more information on CDER's FRAME initiative, see https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/cders-framework-regulatory-advanced-manufacturing-evaluation-frame-initiative.

[8] See, e.g., section 501(a)(2)(B) of the FD&C Act (21 U.S.C. 351(a)(2)(B)) and 21 CFR 211.100.

[9] See ICH Q10.

control unit, during the production process, e.g., at commencement or completion of significant phases or after storage for long periods."

III. GENERAL CONSIDERATIONS FOR IN-PROCESS SAMPLING AND TESTING

Under section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act, a drug is deemed to be adulterated if it is not produced in accordance with CGMP. The CGMP regulations for drug products are in 21 CFR parts 210 and 211, and FDA monitors drug product manufacturers' compliance with these regulations.[10] The CGMP regulations contain minimum requirements for the methods, facilities, and controls used in manufacturing, processing, packing, and holding of drug products. The CGMP regulations also provide flexibility for manufacturers to use better, more efficient methods to meet CGMP requirements because these innovative methods benefit patients.[11] The determination of whether in-process controls, and tests, or examinations meet the regulatory requirements in § 211.110 primarily depends on the nature of the drug product (e.g., dosage form) and the type of process used by the manufacturer. Knowledge and understanding that manufacturers gain from robust product and process development are an important basis for establishing and maintaining control strategies throughout the lifecycle of a drug product. This helps ensure that drug products have the required quality attributes.[12]

To ensure conformance to drug product quality requirements, the manufacturer should identify which critical quality attributes[13] and in-process material attributes to monitor and control. Section 211.110 allows flexibility in the in-process controls, and testing, or examinations that are employed to ensure that processes deliver in-process materials and drug products with the appropriate quality attributes. To ensure that drug products have the properties that they are represented to possess, the in-process materials used throughout the manufacturing process should be of consistent quality.

In addition to identifying which critical quality attributes and in-process material attributes to monitor, the manufacturer should define and justify where and when the proposed in-process controls, and testing, or examinations that are used to monitor those attributes should occur. The definition and justification should be based on the manufacturer's understanding of the product and the process. Under § 211.110(c), "[i]n-process materials shall be tested for identity, strength, quality, and purity as appropriate, and approved or rejected by the quality control unit, during the production process, e.g., at commencement or completion of significant phases or after storage for long periods." As noted in the preamble of the final rule, "Current Good Manufacturing Practice in Manufacture, Processing, Packing, or Holding," FDA declined to define the term *significant phase*.[14] Instead, FDA stated that "significant phases in the processing of drug products can vary greatly depending on the methods used and nature of the individual

[10] Positron emission tomography (PET) drug products are subject to CGMP regulations at 21 CFR part 212 and are not covered by this guidance.

[11] See pages 45020-45021 of the final rule, "Current Good Manufacturing Practice in Manufacture, Processing, Packing, or Holding." (43 FR 45014 September 29, 1978). The preamble to the final rule refers to benefits for consumers. For the purposes of this guidance, the term *consumer* is synonymous with the term *patient*.

[12] See guidance for industry *Process Validation: General Principles and Practices* (January 2011).

[13] For more information about critical quality attributes, see ICH Q8(R2).

[14] See 43 FR 45014 at 45052.

products."[15] Therefore, the regulations generally allow flexibility in the determination of significant phases depending on the manufacturing process and the drug product. Manufacturers should define the significant phases in their manufacturing processes; however, FDA evaluates the adequacy of these determinations and the supporting scientific rationale during application assessment and on inspection. The manufacturer should use a scientific- and risk-based approach to determine what constitutes a significant phase and to justify when and where the appropriate tests or examinations should occur relative to a significant phase. It is important to choose the appropriate in-process controls, and tests, or examinations to ensure the quality of in-process materials as well as the performance of the manufacturing process. Process monitoring and control decisions that result in minor equipment and process adjustments do not typically need additional quality unit[16] approval if all of the following conditions are met: (1) the adjustments are within the preestablished and scientifically justified limits; (2) these limits have been approved by the quality unit in the master production and control record and the control strategy; and (3) the production data is reviewed by the quality unit before approval or rejection of a batch.[17,18]

In-process testing strategies should be dictated by the nature of the drug and the manufacturing processes. Manufacturers should ensure that innovative strategies that streamline in-process testing provide sufficient assurance of product quality. The manufacturer should employ a scientifically sound and appropriate sampling and testing strategy for quality attributes at appropriate points[19] in the process that are adequate to ensure drug product quality. The manufacturer should employ time-based sampling plans for quality attributes, where appropriate (e.g., time-based measurement of the change in dryer outlet temperature during powder drying processes, which can be used as a surrogate measurement for moisture content).

In addition to appropriate flexibility in where and when in-process sampling and testing should occur, the regulations provide flexibility in how in-process material and drug product testing is conducted. The preamble to the final rule states that a sampling plan "can mean both a plan for collection of physical units for testing, or it can mean a schedule by which an examination of some sort is done."[20] Although in-process controls, and tests, or examinations of in-process materials are required,[21] sampling does not necessarily require steps for physically removing in-process materials to test their characteristics. Innovative technologies allow in-line, at-line, or on-line measurements in place of physical sample removal for laboratory testing,[22] and these measurements can be used in conjunction with process models.

---

[15] Ibid.

[16] For the purposes of this guidance, the term *quality unit* is synonymous with the term *quality control unit*. For the definition of *quality control unit*, see § 210.3(b)(15).

[17] Under § 211.100, a manufacturer must have written procedures for production and process control. Such procedures must be reviewed and approved by the quality unit.

[18] See § 211.110(c) and 43 FR 45014 at 45052.

[19] An appropriate point can occur during or after a single manufacturing step or a group of manufacturing steps that the manufacturer has determined to be a significant phase.

[20] See 43 FR 45014 at 45033.

[21] See § 211.110(a).

[22] See guidance for industry *PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance* (October 2004).

IV. ADDITIONAL CONSIDERATIONS FOR ADVANCED MANUFACTURING AND PROCESS MODELS

FDA recognizes that advanced manufacturing can enable pharmaceutical modernization and deliver benefits to both industry and patients. The CGMP regulations generally allow flexibility in how manufacturers can demonstrate compliance. Manufacturers can use a variety of approaches including incorporation of certain advanced manufacturing technologies. Both enhanced pharmaceutical development approaches and real-time quality monitoring of in-process materials (e.g., process analytical technology (PAT),[23] process models) can improve drug product quality and support advanced manufacturing. For example, continuous manufacturing that incorporates enhanced process monitoring generally results in increased process understanding.

Continuous manufacturing and batch manufacturing could have different control strategies to ensure batch uniformity and drug product integrity. Both continuous manufacturing and batch manufacturing generally involve multiple manufacturing steps that physically or chemically transform in-process materials. Typically, with a batch manufacturing process, in-process materials can be easily isolated between each manufacturing step. This allows greater access for sampling and testing of in-process materials before or after each step. However, given the process design for continuous manufacturing, isolating in-process materials may not be feasible.

As described in Section III, § 211.110 provides flexibility in what in-process sampling and testing should be done in addition to where, when, and how it should be done. Drug product manufacturers must use appropriate in-process control, and testing, or examination strategies to ensure that in-process materials can be meaningfully evaluated at significant phases.[24] This evaluation allows the quality unit to make approval or rejection determinations for in-process materials during the production process.[25] Because of the integrated nature of continuous manufacturing processes, the quality unit can make a scientific determination that two or more unit operations can be considered a single significant phase of manufacturing. This decision should be made before initiating manufacturing, and it should be based on process understanding. For example, in batch manufacturing of a solid oral drug product, blend uniformity should typically be assessed before in-process materials continue to the compression step. However, in continuous manufacturing, a manufacturer could conduct sampling and testing at an appropriate point in the process (e.g., at the tablet press feed frame or after compression) to evaluate the adequacy of mixing to ensure batch uniformity and homogeneity. Then, the quality unit can determine whether to approve or reject the in-process material either before or after the compression stage. Manufacturers should have robust understanding of the process, including system dynamics. This will help manufacturers ensure that the sampling frequency is sufficiently representative to draw a statistically valid conclusion about the quality of the in-process materials and the drug product.

---

[23] PAT is a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring drug product quality. See guidance for industry *PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance*.

[24] See § 211.110.

[25] See § 211.110(c) which requires the quality control unit to approve or reject in-process materials during the production process.

Other approaches can also be used to monitor the characteristics of in-process materials and validate the performance of manufacturing steps that may be responsible for causing variability. These other approaches could provide data that supports the quality unit's approval or rejection of in-process materials during the production process. For example, a process model can be used to help monitor the attributes of in-process materials that affect the drug product's critical quality attributes. Process models can be useful for implementing advanced manufacturing, such as continuous manufacturing. Thus, process models can be a component of the overall control strategy. This approach can enhance understanding and control of the manufacturing process.

The behavior of a process can be mathematically represented by a process model. During routine commercial operation, a process model's ability to predict quality attributes of in-process materials depends upon the sufficiency and applicability of the model's underlying assumptions. Therefore, both the adequacy of a process model and its ability to facilitate a maintained state of control are dependent upon the underlying assumptions remaining valid.[26] Advanced manufacturing (such as continuous manufacturing) generally lends itself to more extensive understanding and control of the manufacturing process; thus, it is generally suitable for implementation of process models as part of the control strategy.

FDA is aware of industry's interest in using in-process control strategies that rely solely on process models to satisfy the requirements of § 211.110. This includes interest in strategies that use process models in continuous manufacturing to predict in-process material uniformity and homogeneity without any testing or examination of the in-process material (whether direct or indirect). However, to date, FDA has not been made aware of process models that demonstrate that: (1) the underlying assumptions of the process model will remain valid during routine manufacturing; and (2) the manufacturer can detect if an underlying assumption is no longer valid (e.g., a continuous mixing model that assumes uniform mixing would be unable to detect that uniform mixing is no longer occurring due to material agglomeration on the walls of the mixer). In other words, current process models cannot ensure the continued validity of all of the model's underlying assumptions at all times, particularly during certain unplanned disturbances. In the event of an unplanned disturbance that is not accounted for by the model's underlying assumptions, such control strategies would be unable to prevent nonconforming in-process materials (e.g., nonhomogeneous powder blend) from continuing through production and being used "in manufacturing or processing operations for which they are unsuitable."[27,28] Therefore, control strategies that rely solely on current process models would be insufficient to satisfy the requirements of § 211.110.

Process models, when paired with in-process material testing or process monitoring (including process inputs and outputs), can be powerful tools for maintaining a state of control and ensuring drug product quality. In-process material testing can be achieved either through laboratory testing of a physical sample removed from the process or implementation of other innovative

[26] For more information on the design and validation of process models, see ICH guidance for industry *Q8, Q9, & Q10 Questions and Answers — Appendix Q&As from Training Sessions* (July 2012).
[27] See § 211.110(d).
[28] This would be particularly true of an unplanned disturbance that could affect the model's output without being detected.

technologies or methods which can be at-line, on-line, or in-line. As an alternative to certain in-process tests, process monitoring (e.g., surrogate measurements), where scientifically appropriate, could be acceptable. Process models should incorporate process monitoring or in-process testing to maintain a state of control, facilitate model maintenance, and ensure drug product quality. FDA encourages the use of a scientifically valid combination of modern control strategies to develop and implement effective and innovative approaches in pharmaceutical development, manufacturing, and quality assurance.

As part of FDA's mission to protect and promote the public health, FDA is committed to supporting and enabling pharmaceutical innovation and modernization. As the science supporting innovative in-process control tools and methods continues to develop, FDA anticipates that these scientific advancements can be leveraged to pursue in-process control strategies that increasingly rely on process models. Based on the challenges associated with these approaches, FDA encourages industry representatives and manufacturers to contact FDA if they are interested in using alternative control strategies. Industry representatives and sponsors can contact the Center for Drug Evaluation and Research's Emerging Technology Team,[29] the Center for Biologics Evaluation and Research's Advanced Technologies Team,[30] or the Center for Veterinary Medicine,[31] as appropriate. These strategies should be discussed as early in the development process as possible. These discussions will also help inform future policy development to support the adoption of robust alternative control strategies.

REFERENCES

Guidances for Industry

PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance (October 2004)

Process Validation: General Principles and Practices (January 2011)

ICH Guidances for Industry

Q8, Q9, & Q10 Questions and Answers — Appendix Q&As from Training Sessions (July 2012)

Q8(R2) Pharmaceutical Development (November 2009)

Q9(R1) Quality Risk Management (May 2023)

Q10 Pharmaceutical Quality Systems (April 2009)

Q13 Continuous Manufacturing of Drug Substances and Drug Products (March 2023)

[29] https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/emerging-technology-program
[30] https://www.fda.gov/vaccines-blood-biologics/industry-biologics/cber-advanced-technologies-program
[31] Questions or requests may be sent directly to CVM through email AskCVM@fda.hhs.gov.