



What are the FDA's cGMPs Expectations?

“Can this be cited on an FDA-483?”

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Outline



- Recommendations for keeping up with FDA's cGMP expectations
- Discuss regulations, guidance documents and other useful documents to understand FDA's expectations and processes
- Examples of FDA-483s and Warning Letters

Have you seen this slide before?



Everyone deserves
confidence in their *next*
dose of medicine.

Pharmaceutical quality assures the
availability,
safety,
and efficacy
of *every* dose.



What's the ultimate goal of cGMPs?

- 21 CFR 210 & 21 CFR 211- to produce safe and effective drugs that meet quality standards.
- Have you read the Preamble for the cGMP regulations in the Federal Register?
 - The FDA finalized 21 CFR Part 211 in 1978. The preamble to the regulation explains the FDA's interpretation of the regulation and how it will impact the industry and public. It also responds to comments submitted by the public and industry.
<https://www.fda.gov/files/drugs/published/Federal-Register-43-FR-45077.pdf>
 - The preamble includes:
 - Why the regulation is being proposed
 - The FDA's interpretation of the regulation's meaning and impact
 - The FDA's review and commentary on public comments

Current FDA's cGMP Expectations

Is this clearly written somewhere for every situation? No, but...

- How do you know the current FDA GMP expectations?
 - Federal Register, cGMP preamble
 - FDA Compliance Programs (Examples)
 - CP 7356.002 Drug Manufacturing Inspections
 - 7356.002A Sterile Drug Process Inspections
 - 7356.002M Surveillance Inspections of Protein Drug Substance Manufacturers
 - 7356.002F Active Pharmaceutical Ingredient Process Inspection
 - 7371.001 Animal Drug Manufacturing Inspections

<https://www.fda.gov/drugs/guidance-compliance-regulatory-information/drug-compliance-programs>

Current FDA's cGMP Expectations

Is this clearly written somewhere for every situation? No, but...

- Guidance documents (most current, not withdrawn)
<https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs>
- Example: *Draft* Powder Blends and Finished Dosage Units- Stratified in-process dosage unit sampling and assessment, October 2003 (withdrawn Aug 2013)
- FDA Q&A on cGMP Requirements
<https://www.fda.gov/drugs/pharmaceutical-quality-resources/qa-cgmp-requirements>
- Industry standards (USP, ICH, PIC/S, PDA, ISPE, ASTM, ISO, etc.)
- FDA-483s and Warning Letters



FDA Guidance Documents

Standard Language in Guidance Documents

- This guidance represents 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.
- 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.

New *Draft* Guidance: Considerations for complying with 21 CFR 211.110, Jan 2025

<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-complying-21-cfr-211110>

- This guidance describes considerations for complying with the requirements in § 211.110 (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**.
 - how manufacturers can incorporate process models into commercial manufacturing control strategies.

<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/q13-continuous-manufacturing-drug-substances-and-drug-products>

21 CFR 211.110 *Draft* Guidance



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.



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 implementing 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. However, control strategies that rely solely on current process models would be insufficient to satisfy the requirements of § 211.110.

21 CFR 211.110 Sampling and Testing of In-Process Materials and Drug Products

➤ To assure batch uniformity and integrity of drug products, written procedures shall be established and followed that describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch. Such control procedures shall be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product. Such control procedures shall include, but are not limited to, the following, where appropriate:

(1) Tablet or capsule weight variation; (2) Disintegration time; (3) Adequacy of mixing to assure uniformity and homogeneity; (4) Dissolution time and rate; (5) Clarity, completeness, or pH of solutions, (6) Bioburden testing, etc.

FDA Concerns on Process Models in Continuous Manufacturing

FDA's Awareness Gap:

- Lack of models demonstrating validity of assumptions during routine manufacturing
- Insufficient methods to detect when assumptions become invalid
- Particularly vulnerable during unplanned disturbances

Potential Risks:

- Inability to prevent nonconforming materials in production
- Risk of using unsuitable materials in manufacturing operations

Example:

- Continuous mixing model assuming uniform mixing
- May fail to detect non-uniform mixing due to material agglomeration

FDA's Stance on Process Models in Pharmaceutical Manufacturing



FDA supports pharmaceutical innovation and modernization



Guidance explains how process models can be combined with:

In-process material testing
Process monitoring



Aims to meet current regulatory requirements (21 CFR 211.110)



Evolving In-Process Controls:

Physical sample removal not always necessary
Innovative technologies allow for:
• In-line measurements, at-line measurements, on-line measurements



New measurement methods can be used with process models



Other Useful Documents

Useful Documents

Compliance Policy Guides (CPG)

- What they are: Collection of FDA documents that describes precedents for FDA decision making in several key areas
- Where to find it:
<http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/default.htm>
- How to use it: Help to understand FDA position on common issues that arise and require consistent regulatory response by FDA
- Examples:
 - CPG Sec. 130.300 FDA Access to Results of Quality Assurance Program Audits and Inspections
 - CPG Sec. 490.100 Process Validation Requirements for Drug Products and Active Pharmaceutical Ingredients Subject to Pre-Market Approval

Useful Documents

Regulatory Procedures Manual (RPM)

- What it is: Describes the standards and processes by which all FDA regulatory actions come about
- Where to find it:
<http://www.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/default.htm>
- How to use it: Understand how FDA regulatory decisions are made (such as Warning Letters, product seizures and consent decrees of injunction)
- Examples:
 - Chapter 2, FDA Authority
 - Chapter 4, Advisory Actions (includes Warning Letters)
 - Chapter 6, Judicial Actions (seizures, injunctions, prosecutions)

Useful Documents

Field Management Directives (FMD)

- What it is: Guidance to FDA Field Offices about administrative procedures
- Where to find it:
<http://www.fda.gov/ICECI/Inspections/FieldManagementDirectives/ucm056246.htm>
- How to use it: Help understand how FDA makes decisions about inspection report classification and miscellaneous other issues
- Key Sections:
 - FMD 86, Establishment Inspection Report Conclusions and Decisions
 - FMD 145, Release of the Establishment Inspection Report (EIR)



FDA-483s

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FDA 483s

- *“This document lists observation made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above.”*
- A strategic response to an FDA Form 483 is critical in preventing escalation to a Warning Letter. The cost to remediate observations may be initially high, but a comprehensive approach and investing in a quality culture will achieve compliance.

Can this be cited on an FDA-483?

- FDA needs to understand your scientific rationale for your practices
 - Is your practice compliant with 21 CFR 210 & 211 requirements? “shall” vs “should”
 - Does your practice align or exceed recommendations in FDA guidance documents?
 - Can you defend your actions to ensure product quality standards are consistently met?
 - Process validation, data, risk assessments, development work, continued process verification, etc...
- Do you have all supporting documentation for investigations, CAPAs, risk assessments, rationale, data, etc.?
 - *If it is not documented, it didn't happen...*

FDA Inspection Methodology

A closer look at investigations – what is FDA looking for?

- › Does the firm have an SOP for investigations? Is it followed?
- › Are investigations opened and closed in a timely manner?
- › Does the investigation record basic information? Date discovered, date opened, date closed, lot or process information, description of event, potential root cause, CAPAs (may be in another document), was the investigation extended to other lots/processes are necessary?
- › Is the investigation scientifically sound?
- › Was a root cause(s) identified? – **human error is a red flag to FDA**
- › What method did the firm use to conduct root cause analysis?

FDA Inspection Methodology

A closer look at investigations – what is FDA looking for?

- › Is this a repeat deviation? If so, when was the last investigation opened?
- › If this is a repeat investigation, did the firm implement a CAPA after the previous investigation? If so, why did the issue occur again?
- › Was the previous root cause incorrect? Or was a potential root cause not considered?
- › Did the firm perform forensic testing as needed? (e.g., foreign particle ID)
- › Was any market action required?
- › For the current investigation, were CAPAs implemented and followed up?
- › Does the firm perform CAPA effectiveness check?



FDA's cGMP Expectations and Industry Commitments

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Examples of FDA's Expectations for Remediation

Warning Letters

Issue: Alert and action limits in purified water samples used in oral drug products

- A comprehensive remediation plan for the design, control, and maintenance of the water system
- A comprehensive assessment of the design and control of the firm's manufacturing operations, including a detailed review and thorough review of all microbiological hazards.
- Retrospective review of all released batches manufactured when water sample results were out of specifications.

Issue: Environmental monitoring (EM) excursions and poor aseptic techniques

- Thorough retrospective review and risk assessment that evaluates how poor aseptic technique, cleanroom behavior and EM deviations may have affected the quality and sterility of your drug products.
- A comprehensive, independent risk assessment of all contamination hazards with respect to aseptic processes, equipment, and facilities, including an independent assessment that includes, but is not limited to: all human interactions within the ISO 5 area, equipment placement and ergonomics, air quality in the ISO 5 area and surrounding rooms, facility layout, and personnel and material flows.

Recommendations to meet FDA's cGMP Expectations

- Understand and follow the regulations, 21 CFR 210 & 211
 - Continuous and focused training of ALL employees
- Establish a Mature Quality Culture & Quality Oversight (ICH Q12)
 - Critical thinking, patient-focused
 - Understand your processes' weaknesses and strengths and personnel practices
 - QA oversight of manufacturing, laboratory operations, warehousing, etc.
 - Identify and manage all potential risks (ICH Q9-Quality Risk Management)
- Continuous improvement- Identify, correct, document, and learn from deviations holistically



Thank you

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With Heart™

