



Regulatory Education for Industry (REdI): Focus on CGMPs & FDA Inspections

Sheraton | Silver Spring, MD | July 15-16, 2015

Welcome

**Brenda Stodart, Pharm.D.
Program Director**

CDER Small Business and Industry Assistance (CDER SBIA)



Regulatory Education for Industry (REdI): Focus on CGMPs & FDA Inspections

Sheraton | Silver Spring, MD | July 15-16, 2015

Materials: Basic CGMP Requirements

Presenters:

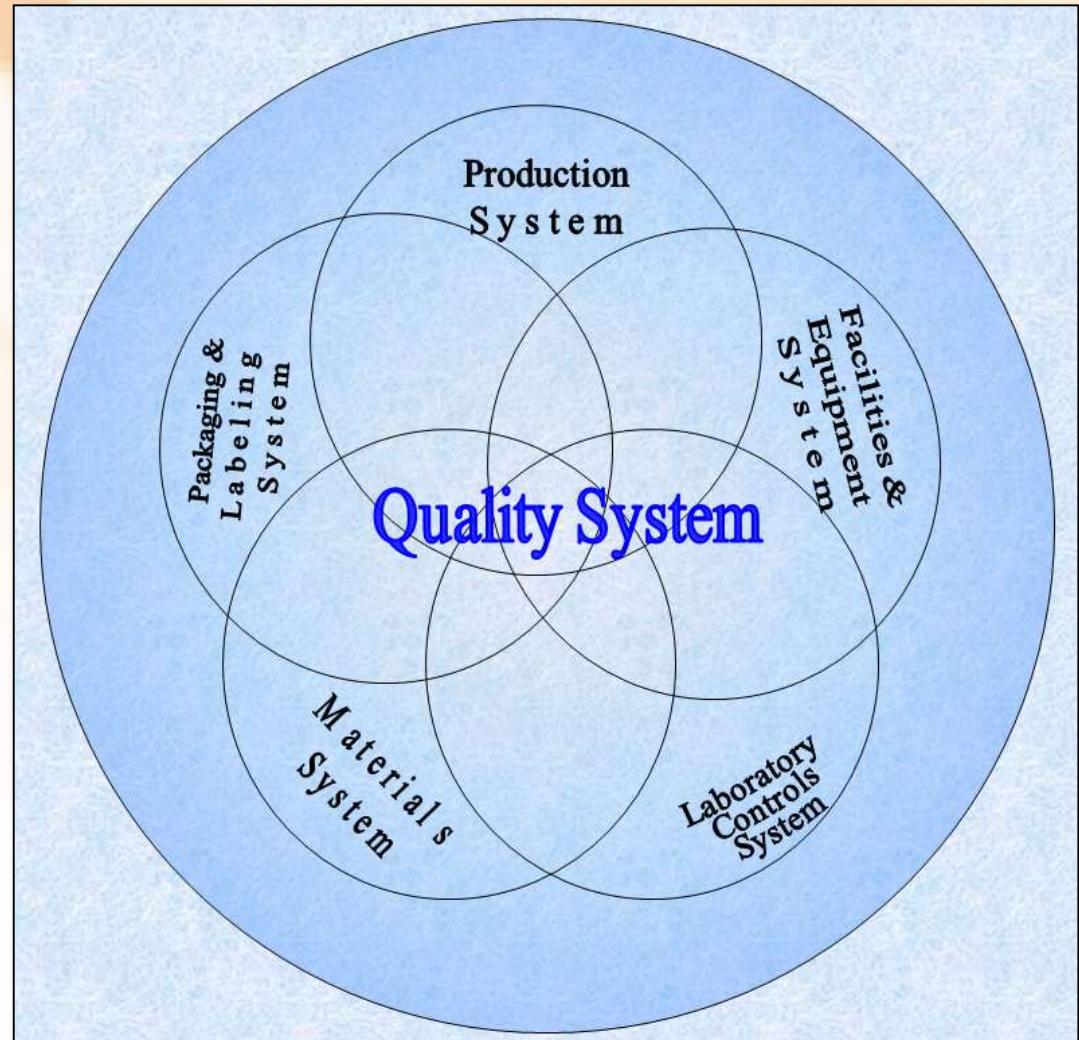
Alicia Mozzachio, R.Ph., MPH
Division Director (Acting) DRGS/OPPQ

Minerva Hughes, Ph.D.
Branch Chief (Acting) DRGS/OPPQ



The Six Components

- Quality
- Production
- Laboratory
- Materials
- Facilities & Equipment
- Packaging & Labeling





Overview

- **Definitions – Materials System**
- **What is covered in the Materials System**
- **Applicable CGMP Regulations**
- **Applicable Guidances**
- **Questions**



Definitions - Important Terms

• Component

- any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product, 21 CFR 210.3(b)(3)
 - Ex. excipients, water, gases, etc., even if not in final product, but excludes the container closure system

• Active Ingredient

- any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, or to affect the structure or any function of the body of man or other animal, 21 CFR 210.3 (b)(7)



Definitions - Important Terms

- **Inactive ingredient (excipient)**

- any component other than an active component, 21 CFR 210.3(b)(8)

- **Containers and Closures**

- Not defined in the CGMP regulations
- Interpreted as the primary packaging of a finished drug product
- May include glass, plastic or metal containers, bottles, vials, ampules, screw caps, lids, stoppers, seals, desiccants, fillers, etc.



What is Covered?

Many areas are involved:

- **Inventory controls and distribution practices**
- **Identification (visual examinations and ID specificity)**
- **Personnel Training/Qualifications**
- **Storage conditions (normal and quarantine)**
- **Representative sampling procedures**
- **Supplier validation and component testing**



What is Covered?

And the list continues...

- Retesting/re-examining materials (documented investigations where necessary)
- Rejecting components, containers and closures
- Change procedures for materials and handling operations
- Water and gas supply, design, maintenance, validation and operation
- First in/First out procedures
- Computerized and automated processes



Applicable CGMP Regulations

21 CFR 211 Subpart B – Organization and Personnel

21 CFR 211 Subpart E – Control of Components and Drug Product Containers and Closures

21 CFR 211 Subpart H – Holding and Distribution

21 CFR 211 Subpart J – Records and Reports



21 CFR 211 Subpart E

- 21 CFR 211.80 General Requirements**
- 21 CFR 211.82 Receipt and Storage**
- 21 CFR 211.84 Testing and approval or rejection**
- 21 CFR 211.86 Use of approved components**
- 21 CFR 211.87 Retesting of approved components**
- 21 CFR 211.89 Rejected components**
- 21 CFR 211.94 Drug Product Containers/Closures**



§211.80 –General Requirements

- (a) There shall be written procedures describing in sufficient detail the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components and drug product containers and closures; such written procedures shall be followed.
- (b) Components and drug product containers and closures shall at all times be handled and stored in a manner to prevent contamination.





§211.80 –General Requirements

- (c) Bagged or boxed components of drug product containers, or closures shall be stored off the floor and suitably spaced to permit cleaning and inspection.
- (d) Each container or grouping of containers for components or drug product containers, or closures shall be identified with a distinctive code for each lot in each shipment received. This code shall be used in recording the disposition of each lot. Each lot shall be appropriately identified as to its status (i.e., quarantined, approved, or rejected).





§211.80 – General Requirements

Topic: Control of Components and Drug Product Containers and Closures

Guidance:

1. [ICH Q9: Quality Risk Management](#)
2. [ICH Q8\(R2\): Pharmaceutical Development](#)

Key Points:

- **Detailed written procedures; followed**
- **Assess, control, communicate, and review (ICH Q9)**
- **Proper storage and identification (ICH Q8(R2))**
 - **Distinctive codes/Traceability**
 - **Status of material (approved, quarantined, or rejected)**



§211.82 – Receipt & Storage

Receipt and storage of untested components, drug product containers, and closures.

- (a) Upon receipt and before acceptance, each container or grouping of containers of components, drug product containers, and closures shall be examined visually for appropriate labeling as to contents, container damage or broken seals, and contamination.
- (b) Components, drug product containers, and closures shall be stored under quarantine until they have been tested or examined, whichever is appropriate, and released. Storage within the area shall conform to the requirements of 211.80.





§211.82 – Receipt & Storage

Topic: Control of Components and Drug Product Containers and Closures

Guidance:

1. [ICH Q10: Pharmaceutical Quality System](#)
2. [Q&A – CGMP, GGP Level 2 Guidance – Control of Components and Drug Product Containers and Closures](#)

Key Points:

- **Evaluate supplier competence; monitor and review performance (ICH Q10)**
- **Policies for prevention and avoidance, not just testing**
- **Should sample after receipt (no pre-shipments)**
- **Beware of composite sampling**



§211.84 – Testing and Approval/Rejection

Testing and approval or rejection of components, drug product containers, and closures.

- (a) Each lot of components, drug product containers, and closures shall be withheld from use until the lot has been sampled, tested, or examined, as appropriate, and released for use by the quality control unit.
- (b) Representative samples of each shipment of each lot shall be collected for testing or examination. The number of containers to be sampled, and the amount of material to be taken from each container, shall be based upon appropriate criteria such as statistical criteria for component variability, confidence levels, and degree of precision desired, the past quality history of the supplier, and the quantity needed for analysis and reserve where required by 211.170.





§211.84 – Testing and Approval/Rejection

(c) Samples shall be collected in accordance with the following procedures: (1-6)

1. Cleaned when necessary
2. Opened, samples and resealed to prevent contamination
3. Aseptic techniques used for sterile equipment
4. Sampling from top, middle, and bottom is not a composite
5. Sample containers identified (material, lot no., container, date, sampler)
6. Containers from which samples have been taken show samples were removed.





§211.84 – Testing and Approval/Rejection (cont.)

(d) Samples shall be examined and tested as follows: (1-6)

1. At least one test to verify identity
2. Each component tested for conformity to all appropriate written specifications (In lieu of testing: at least one specific ID test, established manufacturer reliability, and supplier's COA)
3. Each container/closure tested for to all appropriate written specifications (In lieu of testing: visual identification, established manufacturer reliability, and supplier's COA)
4. Microscopic evaluation when appropriate
5. Components, drug product containers, or closures liable to contamination with filth, insect infestation, or other extraneous adulterant shall be examined against established specifications for such contamination
6. Each lot of a component, drug product container or closure with potential for microbiological contamination that is objectionable in view of its intended use shall be subjected to microbiological tests before use.





§211.84 – Testing and Approval/Rejection (cont.)

(e) Any lot of components, drug product containers, or closures that meets the appropriate written specifications of identity, strength, quality, and purity and related tests under paragraph (d) of this section may be approved and released for use. Any lot of such material that does not meet such specifications shall be rejected.





§211.84 Testing and the Water System

Most ubiquitous component used; purity matters

- Intended use
 - Guidance – Sterile Drug Products Produced by Aseptic Processing – CGMPs (high purity for rinse water)
- Water system validation
 - Guide to Inspections of High Purity Water Systems
- Should use purified water
- USP monographs (minimum standards)
- *Resource: USP <1231> Water for Pharmaceutical Purposes*



§211.84 – Testing & Approval/Rejection

Topic: Control of Components and Drug Product Containers and Closures

Guidance:

1. [Guidance – Container Closure Systems for Packaging Human Drugs and Biologics](#)
2. [ICH Q2\(R1\): Validation of Analytical Procedures](#)

Key Points:

- **Approved suppliers, supply chain control, and verification tests**
- **Sampling protocols in place; followed**
- **Testing criteria linked to product use**
- **Methods fit for purpose (ICH Q2(R1))**



§211.84 – Additional Notes

Uncertainty in the supply chain increases the risks to products and patients.

- Guidance – Heparin for Drug and Medical Device Use: Monitoring Crude Heparin for Quality
- Guidance – Pharmaceutical Components at Risk for Melamine Contamination
- Guidance – Testing of Glycerin for Diethylene Glycol
- Q&A – CGMP, GGP Level 2 Guidance – Control of Components, Containers and Closures



§211.86 – Use of Approved Components

Use of approved components, drug product containers, and closures

Components, drug product containers, and closures approved for use shall be rotated so that the oldest approved stock is used first. Deviation from this requirement is permitted if such deviation is temporary and appropriate.

Key Point:

- FIFO





§211.87 – Retesting of Approved Components

Retesting of approved components, drug product containers, and closures.

Components, drug product containers, and closures shall be retested or reexamined, as appropriate, for identity, strength, quality, and purity and approved or rejected by the quality control unit in accordance with 211.84 as necessary, e.g., after storage for long periods or after exposure to air, heat or other conditions that might adversely affect the component, drug product container, or closure





§211.87 – Retesting of Approved Components

Topic: Control of Components and Drug Product Containers and Closures

Guidance:

1. [ICH Q9: Quality Risk Management](#)
2. [ICH Q10: Pharmaceutical Quality System](#)
3. [ICH Q7: Active Pharmaceutical Ingredients*](#)

Key Points:

- **Adopt a lifecycle approach for materials**
- **Risk-based procedures**



§211.89 – Rejected Components

Rejected components, drug product containers, and closures.

Rejected components, drug product containers, and closures shall be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing operations for which they are unsuitable





§211.94 – Containers/Closures

Drug product containers and closures

- (a) Drug product containers and closures shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug beyond the official or established requirements.
- (b) Container closure systems shall provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of the drug product.





§211.94 – Containers/Closures

(c) Drug product containers and closures shall be clean and, where indicated by the nature of the drug, sterilized and processed to remove pyrogenic properties to assure that they are suitable for their intended use. Such depyrogenation processes shall be validated.

(d) Standards or specifications, methods of testing, and, where indicated, methods of cleaning, sterilizing, and processing to remove pyrogenic properties shall be written and followed for drug product containers and closures





§211.94 – Containers/Closures

Topic: Control of Components and Drug Product Containers and Closures

Guidance:

1. [Guidance – Container Closure Systems for Packaging Human Drugs and Biologics](#)
2. **USP <1117> Good Packaging Practices**

Key Points:

- **Verified compatibility/suitability for use**
- **Store, transport, and distribute appropriately**



21 CFR 211 Subpart H

21 CFR 211.142 Warehousing procedures

21 CFR 211.150 Distribution procedures



§211.142 – Warehousing Procedures

Written procedures describing the warehousing of drug products shall be established and followed. They shall include:

- (a) Quarantine of drug products before release by the quality control unit.
- (b) Storage of drug products under appropriate conditions of temperature, humidity, and light so that the identity, strength, quality, and purity of the drug products are not affected.





§211.150 – Distribution Procedures

Written procedures shall be established, and followed, describing the distribution of drug products. They shall include:

- (a) A procedure whereby the oldest approved stock of a drug product is distributed first. Deviation from this requirement is permitted if such deviation is temporary and appropriate.
- (b) A system by which the distribution of each lot of drug product can be readily determined to facilitate its recall if necessary.





21 CFR 211 Subpart J

21 CFR 211.180 General Requirements

21 CFR 211.184 Components, Drug Product Container, Closure, and Labeling Records



§211.180 – General Requirements

- (a) Any production, control, or distribution record that is required to be maintained in compliance with this part and is specifically associated with a batch of a drug product shall be retained for at least 1 year after the expiration date of the batch or, in the case of certain OTC drug products lacking expiration dating because they meet the criteria for exemption under 211.137, 3 years after distribution of the batch.
- (b) Records shall be maintained for all components, drug product containers, closures, and labeling ...
- (c) Records ...shall be readily available for authorized inspection during the retention period at the establishment where the activities ... occurred...





§211.180 – General Requirements

(d) Records required under this part may be retained either as original records or as true copies such as photocopies, microfilm, microfiche, or other accurate reproductions of the original records...

(e) Written records required by this part shall be maintained so that data therein can be used for evaluating, at least annually, the quality standards of each drug product to determine the need for changes and shall include provisions for:

- (1) A review of a representative number of batches...
- (2) A review of complaints, recalls, returned or salvaged drug products, and investigations...





§211.180 – General Requirements

Topic:

Records and Reports

Guidance:

1. [Part 11, Electronic Records: Electronic Signatures - Scope and Application](#)

Key Points:

- **Applies to all components, containers, closures, and labeling**
- **General retention time of 1 year post expiry, unless OTC**
- **Validated computerized systems (part 11), also part of Facilities and Equipment System (§ 211.68)**



§211.184 – Materials Management Records

Component, drug product container, closure, and labeling records

These records shall include the following:

- (a) The identity and quantity of each shipment of each lot of components, drug product containers, closures, and labeling; the name of the supplier; the supplier's lot number(s) if known; the receiving code as specified in 211.80; and the date of receipt. The name and location of the prime manufacturer, if different from the supplier, shall be listed if known.

- (b) The results of any test or examination performed (including those performed as required by 211.82(a), 211.84(d), or 211.122(a)) and the conclusions...





§211.184 – Materials Management Records

- (c) An individual inventory record of each component, drug product container, and closure and, for each component, a reconciliation of the use of each lot of such component. The inventory record shall contain sufficient information to allow determination of any batch or lot of drug product associated with the use of each component, drug product container, and closure.
- (d) Documentation of the examination and review of labels and labeling for conformity with established specifications in accord with 211.122(c) and 211.130(c).
- (e) The disposition of rejected components, drug product containers, closure, and labeling.





Summary

- **Maintain inventory control**
- **Prevent contamination**
- **Know suppliers and supply chain**
- **Appropriate sampling and testing**
- **Written and approved procedures**
- **Ensure compatibility/suitability of containers and closures**

Questions?

Evaluation: [surveymonkey.com/r/CGMP-D2S1](https://www.surveymonkey.com/r/CGMP-D2S1)