



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

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

Laboratory: Laboratory Controls

Presenter:

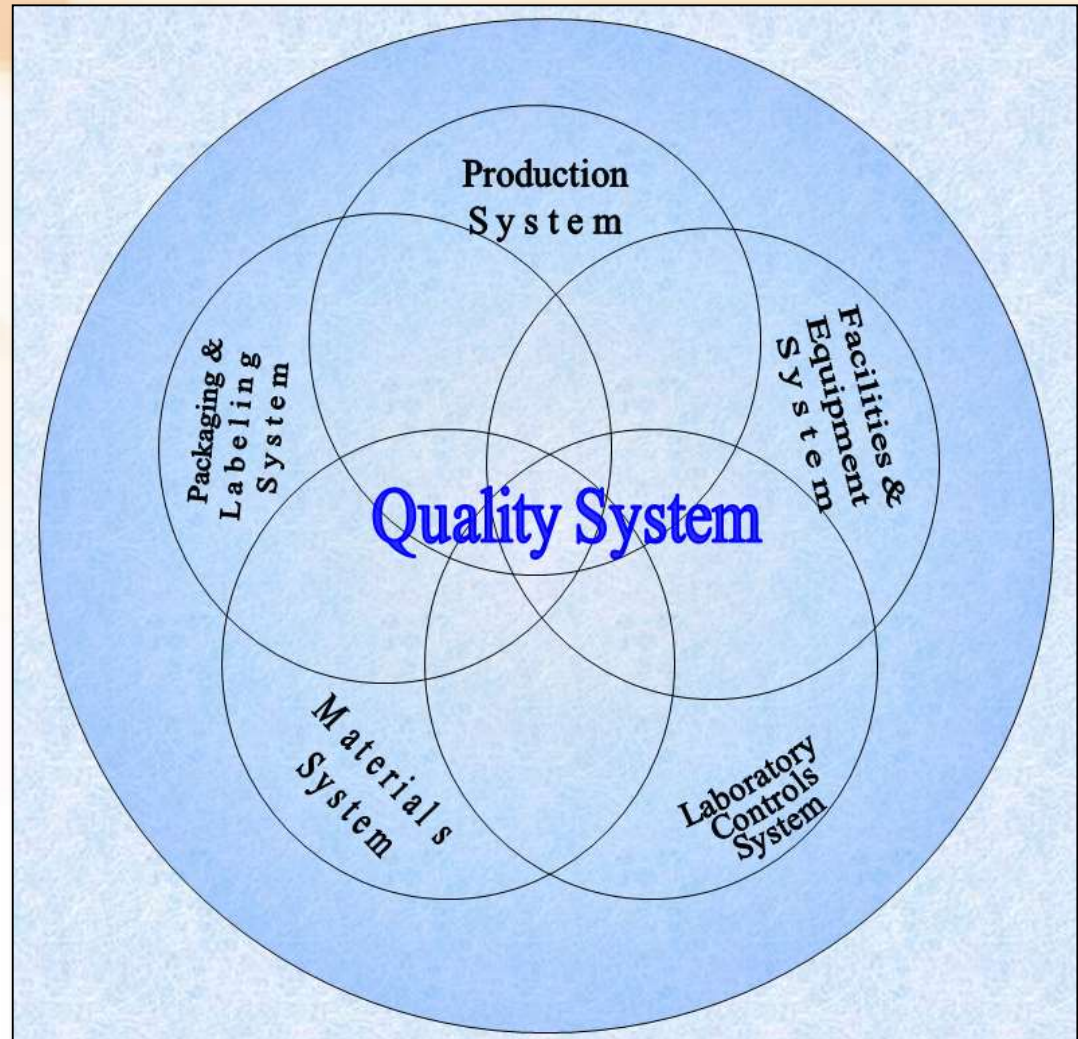
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The Six Systems

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





Overview

- **General Laboratory Requirements**
- **Testing, Approval/Rejection of Components**
- **Testing and Release for Distribution**
- **Stability Testing**
- **Reserve Samples**
- **Laboratory Records**
- **Questions**



§211.160 – General Requirements



General Requirements:

a) Laboratory Controls:

- “shall include the establishment of *scientifically sound and appropriate* specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling, and drug products conform to appropriate standards of *identity, strength, quality, and purity*”

b) Establishment of specifications, standards, sampling plans, and test procedures that must be: *written, approved, documented, justified*

c) Sampling and testing procedures used for: *components, each lot, in-process materials, drug products*

d) Calibration at suitable intervals of Instruments, Apparatus, Gauges, Recording devices, with *written procedures*



§211.160 – Regulation & Key Points

Topic:

General Requirements

Guidance:

1. [ICH Q2A](#) Text on Validation of Analytical Procedures
2. [ICH Q2B](#) Validation of Analytical Procedures: Methodology

Key Points:

- **Scientifically sound and appropriate specs**
- **Establish written specs, sampling, procedures**
- **Conformity to written specifications**
- **Calibration of instruments**



§211.160 – Additional Points

- **Conformance to appropriate standards of identity, strength, quality, & purity**
- **Test results documented at the time of performance**
- **Appropriate procedures for acceptance of components, in-process materials, and drug products**
- **Methods must be documented and approved**



§211.84 – Testing and Approval or Rejection of Components



Testing and Approval or Rejection of Components:

a) Withhold from use:

- Each lot of component, drug product containers, and closures until the lot has been sampled, tested, or examined and released for use

b) Sampling:

- Representative sampling from each shipment of each lot based on appropriate criteria, e.g., statistical criteria, confidence levels, degree of precision desired, quality history of the supplier, quantity needed for analysis.

c) Testing - Components

- At least one test must be conducted to verify the identity of each component of a drug.
- Specific identity tests shall be used if they exist



§211.84 – Regulation & Key Points

Topic:

Testing and Approval or Rejection of Components

Regulation:

1. [CGMP 21 CFR 211.84](#)

Key Points:

- Representative sample consists of a number of units that are drawn based on rational criteria such as random sampling and intended to assure that the sample accurately portrays the material being sampled.
- At least one specific identity test is conducted on the component by the manufacturer at the time of receipt.
- The manufacturer establishes the reliability of the supplier's analysis by validating the supplier's test results at appropriate intervals.



§211.84 – Additional Points

- **Testing for Contamination**
 - **Components...liable to contamination with filth, insect infestation, or other extraneous adulterant shall be examined against established specifications for such contamination**
- **Approval or Rejection of Components**
 - **Components...may be approved and released if they meet all appropriate specifications**
 - **Any lot that does not meet specifications shall be rejected**
 - **Any lot not meeting specifications cannot be used to manufacture a drug product**



§211.110 – Sampling & Testing of In-process Materials & Drug Products



Sampling and Testing of In-process Materials and Drug Products:

- a) To assure batch uniformity and integrity of DPs, in-process control tests shall include, but are not limited to, the following, where appropriate:
- Tablet weight variation;
 - Disintegration time;
 - Dissolution time and rate;
 - Clarity, completeness, or pH of solutions



§211.110 – Regulation & Key Points

Topic:

Sampling and Testing of In-process Materials and Drug Products

Guidance:

1. [ICH Q4B Annex 5: Disintegration Test General Chapter](#)
2. [Use of Mechanical Calibration of Dissolution Apparatus 1 and 2 – CGMP](#)
3. [Development and Submission of NIR Analytical Procedures](#)

Key Points:

- Written procedures shall be established and followed for in-process testing
- In-process materials shall be tested for identity, strength, quality, and purity, and approved or rejected by the QU
- Testing of samples shall assure that the drug product and in-process material conform to specifications



§211.165 – Testing and Release for Distribution



Testing and Release for Distribution:

- a) Each batch of drug product must be tested to determine satisfactory conformance to final specifications, including the *identity and strength of each active ingredient*, prior to release.
- b) Drug products failing to meet established standards or specifications and any other relevant quality control criteria *must be rejected*.
- c) Established and documented accuracy, sensitivity, specificity, and reproducibility of test methods.
- d) Sampling method and number sampled for any sampling and testing plans described in *written procedures*.



§211.165 – Regulation & Key Points

Topic:

**Testing and
Release for
Distribution**

Guidance:

1. [CGMP 21 CFR 211.165](#)

Key Points:

- Documented accuracy, sensitivity, specificity, and reproducibility of test methods
- Test each batch for conformance to specifications
- Follow written sampling and testing plans
- Document testing methods and number of units/batch



§211.165 – Additional Points

- Adequate acceptance criteria for sampling and testing to assure that drug products meet each,
 - Appropriate specification and
 - Appropriate statistical quality control criteria prior to approval and release.



§211.166 – Stability Testing



Drug Product Stability Testing:

- a) Assesses the stability characteristics of *drug products* and determines appropriate storage conditions and expiration dates
- b) Ongoing testing of representative batches to verify product stability during the marketing period of a drug product
- c) Test methods must be *validated and stability-indicating*
- d) A *written testing program* documenting sample storage conditions, sample sizes, and testing intervals
- e) Evidence to support the labeled expiration date



§211.166 – Regulation & Key Points

Topic:

Stability Testing

Guidance:

1. [ICHQ1A](#) Stability Testing of New APIs & DPs
2. [ICH Q1C](#) Stability Testing for New Dosage Forms
3. [ICH Q1D](#) Bracketing & Matrixing Designs...
4. [ICH Q1E](#) Evaluation of Stability Data

Key Points:

- Written stability testing program
- Full shelf-life studies for determining the expiration date
- Combination of accelerated studies and basic stability
- Conducted on samples from representative batches
- Sample size and test intervals based on statistical criteria



§211.166 – Additional Points

- **Product stability is influenced by formulation, manufacturing process, container & closure system, API and excipient sources, storage conditions.**
- **When any of these change, manufacturers must evaluate the impact to product stability.**
- **If applicable, testing in the reconstituted and un-reconstituted product forms.**
- **Recommend on-going periodic verification of stability by adding one batch per year.**



§211.170 – Reserve Samples



Reserve Samples:

- a) Appropriately identified reserve samples must be retained that are representative of each lot in each shipment of each *active ingredient*
- b) Reserve samples must be retained that are representative of each lot or batch of *drug product*, and stored under *conditions consistent with product labeling* and in the marketed immediate container-closure system
- c) Shall be examined visually *at least once a year* for evidence of deterioration
- d) Results of the examination shall be recorded and maintained with other stability data on the drug product



§211.170 – Regulation & Key Points

Topic:

Reserve Samples

Regulation:

1. [CGMP 21 CFR 211.170](#)

Key Points:

- Reserve samples from representative sample lots or batches
- Stored under conditions consistent with product labeling
- Results of the examination shall be recorded and maintained with other stability data on the drug product
- Investigate any evidence of reserve sample deterioration



§211.170 – Additional Points

- Reserve samples consist of at least twice the quantity necessary for all tests required to determine whether the active ingredient/drug product meets its established specifications
- Drug product reserve samples generally must be maintained for one year after the expiration date for the drug product
- Active ingredient samples must be kept for one year after the expiration date for the last lot of the drug product containing the active ingredient



§211.194 – Laboratory Records



Laboratory Records:

- a) Laboratory records shall include *complete data* derived from *all tests* necessary to assure compliance with established specifications and standards
- b) Records must include:
 - All calculations with units
 - Test results and comparison with established standards
 - Initials or signature of analyst and date
 - Initials or signature of a second person
 - Testing results of standard/reagent solutions
 - Calibration and stability testing



§211.194 – Regulation & Key Points

Topic:

Laboratory Records

Regulation:

1. [CGMP 21 CFR 211.194](#)

Key Points:

- A description of the sample
- The location of the method validation data
- A description of the suitability of the method
- Record of the sample weight including all test data obtained
- A statement that test methods are accurate, reliable, and followed



§211.194 – Additional Points

- A statement that the suitability of test methods used was verified under actual conditions of use
- A record of all calculations performed in connection with the test
- A complete record of all data in the course of each test
 - “all data” includes not only test results but also metadata associated with computerized data analysis which is archived and audited by the QU to ensure data integrity



Special Concerns

- [Guidance for Industry](#) - Testing of Glycerin for Diethylene Glycol (May 2007)
- [Guidance for Industry](#) - Pharmaceutical Components at Risk for Melamine (Aug 2009)
- [Guidance for Industry](#) - Heparin for Drug and Medical Device Use: Monitoring Crude Heparin for Quality (June 2013)



Summary

- **General Laboratory Requirements – 211.160**
- **Components Testing, approval/rejection – 211.84**
- **Testing and Release for Distribution – 211.165**
- **Stability Testing – 211.166**
- **Reserve Samples – 211.170**
- **Laboratory Records – 211.194**



Take Home Message

Good Laboratory Controls Help Establish and Maintain a State of Control to Assure Product Quality

A good laboratory system helps to:

- **Ensure consistency of components, including processing aids, and containers/closures**
- **Verify the quality of in-process materials and finished product**
- **Ensure an accurate product shelf-life**
- **Detect and correct deficiencies**
- **Provide consistent product quality**



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

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Laboratory: Microbiology Testing

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Overview-Microbiology Lab Tests

- **Sterility Testing**
- **Bacterial Endotoxins Testing**
- **Antimicrobial Effectiveness Testing**
- **Viral Testing**
- **Container Closure Integrity Testing**
- **Microbial Enumeration:Non-Sterile Drugs**
- **Alternative Microbiological Testing**



§211.167 - Abbreviated

Special Testing Requirements:

a) For each batch of DP purporting to be sterile:

- There shall be an appropriate laboratory sterility test
- The test procedures shall be in writing and followed





§211.167 – Guidance & Key Points

Topic:

Special Testing Requirements-Sterility

Guidance:

1. [Sterilization Process Validation Guidance](#)
2. [Aseptic Processing Guidance](#)
3. [Parametric Release Guidance](#)

Key Points:

- **USP <71> is the Compendial Method**
- **Methods that differ from USP<71> should be demonstrated as equivalent to or better than**



§211.167 – Additional Points- Sterility Test

- **USP<71> Key Points:**
 - **Two methods: Membrane Filtration & Direct Inoculation**
 - **Table 2: Minimum quantity of product to be tested**
 - **Table 3: Minimum number of units to be tested**
 - **Suitability of use of test with product (important)**



§211.167 - Abbreviated

Special Testing Requirements:

- a) For each batch of DP purporting to be pyrogen-free:
- There shall be an appropriate laboratory test
 - The test procedures shall be in writing and followed





§211.167 – Guidance & Key Points

Topic:

**Special Testing Requirements-
Pyrogens**

Guidance:

1. [Sterilization Process Validation Guidance](#)
2. [Pyrogen and Endotoxins Testing Guidance](#)

Key Points:

- **USP <85> is the Compendial Method**
- **Methods that differ from USP<85> should be demonstrated as equivalent to or better than**



§211.167 – Additional Points- Pyrogens Test

- **USP<85> Key Points**
 - **Three methods: Gel Clot, Turbidometric & Chromogenic**
 - **Equation for determination of endotoxin limit**
 - **Equation for determination of MVD of sample**
 - **Suitability of use of test with product (important)**



§211.160(b) - Abbreviated

Lab Controls-General Requirements:

- b) Lab controls shall include appropriate specifications...and test procedures to assure:
- The drug product conforms to appropriate quality standard





§211.160(b) – Guidance & Key Points

Topic:

**General
Requirements-
Multiple Dose
Products**

Guidance:

1. [Sterilization Process Validation Guidance](#)

- **Some drug products are labeled “multiple dose”**
- **Container entered > once for administration**
- **Drug either includes a preservative or is self-preserving**
- **USP<51> Antimicrobial Effectiveness Testing**
- **After initial demonstration of AET, product batches may be tested for chemical content at release and stability**



§211.160(b) – Additional Points- Antimicrobial Effectiveness Test

- **USP<51> Key Points:**
 - **Product is challenged with a panel of microbes**
 - **Microbe counts measured at intervals to include 28 days**
 - **Table 1: Compendial Product Categories**
 - **Table 2: Challenge Microbe Preparation**
 - **Table 3: Test Acceptance Criteria**



§211.160(b) – Guidance & Key Points

Topic:

**General
Requirements-Viral
Testing**

Guidance:

1. [ICH Q5A Viral Safety Evaluation Guidance](#)

- **Drug Products derived from biological origin**
 - **Human or animal tissue/cell lines**
- **Testing for viruses may be appropriate**



§211.160(b) – Additional Points- Viral Testing

- **ICH Q5 Key Points:**
 - **Potential sources of viral contamination**
 - **Testing for viruses to qualify cell line**
 - **Testing for viruses in unprocessed bulk**
 - **Recommended viral detection and identification assays**



§211.160(b) - Abbreviated

Lab Controls-General Requirements:

- b) Lab controls shall include appropriate specifications...and test procedures to assure:
- The drug product containers, closures...
...and the drug product conform to appropriate quality standard





§211.160(b) – Guidance & Key Points

Topic:

**General
Requirements-
Container Closure
Integrity**

Guidance:

1. [Sterilization Process Validation Guidance](#)
2. [CCI in Lieu of Sterility Test Guidance](#)

- **Sterile drug products should maintain a microbial barrier throughout shelf life**
- **There is no compendial container/closure integrity test**
- **USP<1207> offers some guidance**



§211.160(b) – Additional Points- Container Closure Integrity Test

- **Container Closure Integrity Key Points:**
 - **Applicants use a variety of methods**
 - **Microbial ingress, dye ingress, others**
 - **Challenge of drug product should include stress of sterilization process**
 - **Include positive and negative controls**
 - **Demonstrate sensitivity**



§211.165- Abbreviated

Testing and release for distribution:

b) There shall be appropriate laboratory testing:

- Drug product required to be free of objectionable organisms
- §211.165(b) is the laboratory determination of:
 - [§211.113 Control of microbiological contamination](#)
 - Appropriate procedures to prevent objectionable microorganisms in non-sterile drug products





§211.165 – Guidance & Key Points

Topic:

**Testing for Release-
Objectionable
Microbes & Non-
Sterile Drugs**

Guidance:

- **USP<61>**
- **USP<62>**
- **USP<1111>**



§211.165 – Additional Points- Objectionable Microorganisms

- **USP<111>**
 - **Suggested acceptance criteria for microbial counts based on route of administration**
- **USP<61>**
 - **Test method for total microbial counts**
- **USP<62>**
 - **Test method for specified microbes**



Alternative Microbiological Testing

- **Why alternative methods?**
 - **Conventional methodology takes a long time**
- **What is needed for adoption of alternative?**
 - **Demonstration that the alternative method is equal to or better than the compendial test**



Alternative Microbiological Testing

- **How to demonstrate that the alternative method is equal to or better than the compendial test?**
 1. **Validate: alternate method works**
 2. **Demonstrate: suitable for use with product**



Alternative Microbiological Testing

- **No Existing FDA Guidance**
- **Potential Useful Resources**
 - **USP<1223>**
 - **PDA Technical Report 33**



Summary

- **Microbiological testing of drug products**
 - **Sterility, Bacterial Endotoxins, Antimicrobial Effectiveness, Viruses, Container Closure Integrity and Microbial Enumeration**
- **FDA allows alternative test method**
 - **Appropriate validation and suitability**



Take Home Message

The Laboratory System Includes Micro Testing:

- *Appropriate for use*
- *In writing and followed*
- *Validated*
- *Verified to be suitable for use with drug product*

Questions?

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Evaluation: surveymonkey.com/r/CGMP-D1S4