

Preparation For the CPGP (ASQ Certified Pharmaceutical GMP Professional) Exam

4/13/2011

Agenda

- Introduction
- Why Pursue Certification?
- Requirements for Taking test
- Body of Knowledge/Test Question Topics
- References (Good References and where to find them)
- Study Methods
- Handouts and Discussion of Pharmaceutical topics
- Practice Test

Introductions

- Name, Who you work for

Reasons For Certification

- Competing in the Job Market
- Certification may help in Changing Careers (getting into a field where you don't have a lot of experience)
- Broadening knowledge of the pharmaceutical industry

What are your reasons for pursuing certification?

About the test

Requirements

- You must have five years of on-the-job experience in one or more of the areas of the Certified Pharmaceutical GMP Professional Body of Knowledge. A minimum of three years of this experience must be in a decision-making position. “Decision-making” is defined as the authority to define, execute, or control projects/processes and to be responsible for the outcome. This may or may not include management or supervisory positions.
- No Educational Waivers for this Exam

Body of Knowledge for CPGP Exam

- <http://asq.org/certification/pharmaceutical-gmp/bok.html>

Body of Knowledge

- The scope of the exam is broad so take the body of knowledge and suggested reference list at the ASQ site seriously.
- FDA, EU, Japanese, Canadian regulations
- Enforcement Actions
- FDA, ICH, WHO Guidances
- API, Finished Drugs, Biologics
- Manufacturing, Laboratories, Facilities and equipment, raw materials, submissions, distribution, storage, reporting, record retention, sample retention, software, critical parameters
- US Pharmacopeia
- Quality Systems
- Installation Qualification, Operational Qualification, Performance Qualification
- Development
- Much more.....

Test Question Topics

- Regulatory Governance 15 questions
- Quality Systems 30 questions
- Laboratory Systems 30 questions
- Infrastructure (facilities, equipment, utilities) 18 questions
- Sterile and Non sterile manufacturing 25 questions
- Material and Supply Chain management 15 questions
- Filling, Packaging, Labeling 17 questions
- Product Development and Technology Transfer 10 questions

Preparation Methods

- Get copies of the recommended references (make sure that in addition to the various pharmaceutical related references, you bring your most useful QA related references or primers)
- Make sure you have a good subject index
- Make sure your materials are organized so that you can find information easily.
- Allow time (several weeks) to read and study materials and make notes
- Create summary sheets for information that you want to be able to find easily
- Use the ASQ Question Bank (\$99).

What tips do you have concerning preparation for certification tests?

References

Where Many Reference Materials Can be found

- Check ASQ (American Society for Quality) site
- <http://asq.org/certification/pharmaceutical-gmp/references.html>
- For the FDA (Food and Drug Administration) regulations:
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm>
- ICH (International Council on Harmonization) documents:
<http://www.ich.org/products/guidelines> or
<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm065005.htm>
- IPEC (International Pharmaceutical Excipient Council) Guidance Documents <http://ipecamericas.org/content/download-ipec-guidance-documents-here>
- PIC/S (Pharmaceutical Inspection Council and Pharmaceutical Inspection Cooperations Scheme) <http://www.picscheme.org/>
- FDA Investigations Operations Manual
<http://www.fda.gov/ICECI/Inspections/IOM/default.htm>

CFR - Code of Federal Regulations Title 21



510(k) | Registration & Listing | Adverse Events | Recalls | PMA | Classification | Standards
CFR Title 21 | Radiation-Emitting Products | X-Ray Assembler | Medsun Reports | CLIA

Search CFR Title 21 Database Help | More About 21CFR

There are 2 kinds of searches available: Enter a *Part & Section Number*
OR
select a *CFR Part* or a *Full-Text Search*. You may also combine the *CFR Part* and the *Full Text Searches*

Title21 Part.Section (e.g., 862.1385)

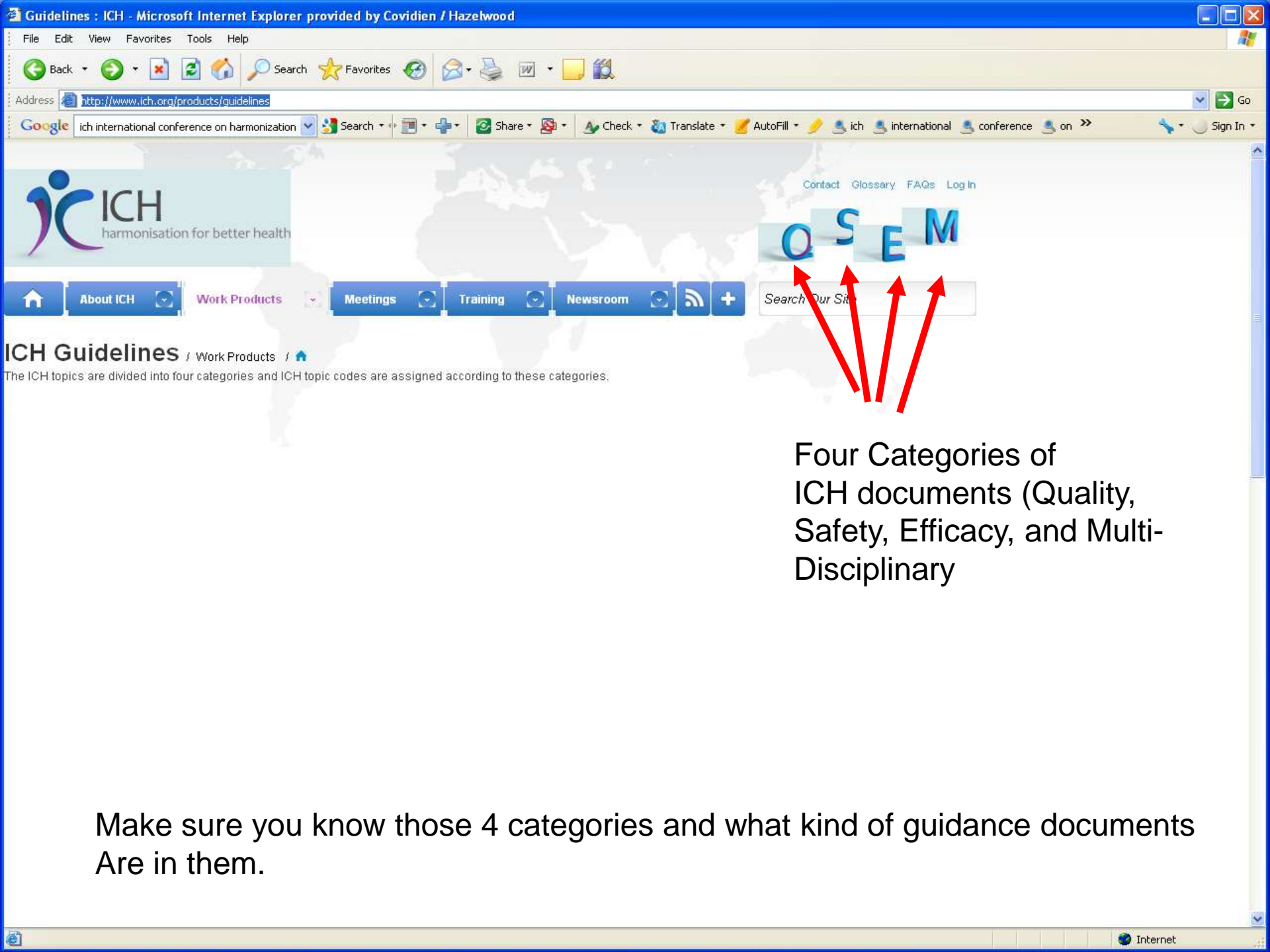
CFR Title 21 - Food and Drugs: Parts 1 to 1499

- (208) Medication guides for prescription drug products
- (209) Requirement for authorized dispensers and pharmacies to dist ...
- (210) Current good manufacturing practice in manufacturing, proces ...**
- (211) Current good manufacturing practice for finished pharmaceuti ...
- (212) Current good manufacturing practice for positron emission to ...

Full Text Search:

Enter a single word (e.g., catheter), an exact phrase (e.g., catheter line) or multiple words connected by *and* (e.g., catheter and tubing).

Page Last Updated: 04/01/2010



Four Categories of ICH documents (Quality, Safety, Efficacy, and Multi-Disciplinary)

Make sure you know those 4 categories and what kind of guidance documents Are in them.

Eudralex (Vol 4) (European Union Rules)

http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm

The screenshot shows a Microsoft Internet Explorer browser window displaying the EudraLex website. The address bar shows the URL: http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm. The page title is "Reference documents - EudraLex - Volume 4 Good manufacturing practice (GMP) Guidelines".

The main content area features a header with the text "Reference documents" and a navigation bar with a "Go back to" link. Below this, the title "EudraLex - Volume 4 Good manufacturing practice (GMP) Guidelines" is displayed, followed by a paragraph explaining that Volume 4 contains guidance for the interpretation of GMP principles and guidelines for medicinal products for human and veterinary use.

The page includes an "Introduction" section with a list of links to various documents, including:

- [Introduction](#) (33 kB) (7/02/2011)
- [Commission Directive 2003/94/EC](#), of 8 October 2003, laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use. Replacement of Commission Directive [91/356/EEC](#) of 13 June 1991 to cover good manufacturing practice of investigational medicinal products.
- [Commission Directive 91/412/EEC](#) of 23 July 1991 laying down the principles and guidelines of good manufacturing practice for veterinary medicinal products.

The page also features a "Part I - Basic Requirements for Medicinal Products" section with a list of chapters:

- [Chapter 1](#)
 - [Quality Management \(revision October 2005\)](#) (23 kB)
 - [Quality Management \(revision February 2009\) - Coming into operation by 01 July 2009](#) (29 kB)
- [Chapter 2 Personnel](#) (20 kB)
- [Chapter 3 Premises and Equipment](#) (34 kB)
- [Chapter 4 Documentation \(Revision January 2011\) - Coming into operation by 30 June 2011](#) (33 kB) **NEW**
 - [Chapter 4 Documentation \(2004\)](#) (27 kB)
- [Chapter 5 Production](#) (50 kB)
- [Chapter 6 Quality Control \(revision October 2005\)](#) (33 kB)
- [Chapter 7 Contract Manufacture and Analysis](#) (22 kB)
- [Chapter 8 Complaints and Product Recall \(revision December 2005\)](#) (18 kB)
- [Chapter 9 Self Inspection](#) (11 kB)

The left sidebar contains a "Reference documents" section with a list of links to various EudraLex volumes, including "Vol 4: GMP Human & Veterinary", which is currently selected. Other links include "EU Legislation - Eudralex", "Vol 1: Legislation Human", "Vol 2: Notice to Applicants Human", "Vol 3: Guidelines Human", "Vol 5: Legislation Veterinary", "Vol 6: Notice to Applicants Veterinary", "Vol 6: MRL Veterinary", "Vol 8: Pharmacovigilance Human & Veterinary", "Vol 10: Clinical Trials", "EudraLex on CD Version 22 - April 2010", and "Vol 7: Medicinal Products Veterinary".

<http://www.gmp-publishing.com/en/>

\$995paper, also have corporate licenses for online version

GMP cGMP (current Good Manufacturing Practice) - Microsoft Internet Explorer provided by Covidien / Hazelwood

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- Technology Transfer
- Chinese Drug GMP

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The GMP MANUAL is used by more than 10,000 professionals in over 65 countries around the world. How do customers experience working with the GMP MANUAL? [Read more...](#)

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ISPE Good Practice Guides

http://www.ispe.org/cs/ispe_good_practice_guides_section/ispe_good_practice_guides

ASQ's question bank references these (If you are not a member of ISPE, these guides are very expensive)

The screenshot shows a Microsoft Internet Explorer browser window displaying the ISPE Good Practice Guides website. The browser's address bar shows the URL: http://www.ispe.org/cs/ispe_good_practice_guides_section/ispe_good_practice_guides. The website header features the ISPE logo with the tagline "Connecting a World of Pharmaceutical Knowledge" and a search bar. The main content area is titled "Publications" and "ISPE Good Practice Guides". A descriptive paragraph explains that GPGs provide information or advise on a particular topic area and explain underlying technical principles. A list of links for various guides is provided, including "Assessing the Particulate Containment Performance of Pharmaceutical Equipment", "Commissioning and Qualification of Pharmaceutical Water and Steam Systems", "Development of Investigational Therapeutic Biological Products", "Good Engineering Practice", "Heating, Ventilation, and Air Conditioning (HVAC)", "Maintenance", and "Technology Transfer". A yellow callout box encourages joining ISPE for member pricing. The right sidebar contains a "Monthly Member Gift" button, "Web Site Sponsors" (including bteo and EAS), and a "Laboratory & Pharmaceutical grade gases" advertisement. The browser's taskbar at the bottom shows the Start button and several open applications, including Microsoft Outlook, a document, Microsoft PowerPoint, and the ISPE Good Practice Guides page.

ASQ's Question Bank

Outstart Learning - Microsoft Internet Explorer provided by Covidien / Hazarwood

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Address http://[ip],outstart.com/aspde/index.htm?themeID=asq&actionCount=1&actionID=com.substart.portal.action.LoginAction&userid=63478477

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ASQ
The Global Voice of Quality

Member Log Out

Gail Keefe

Table of Contents

Certified Pharmaceutical GMP Professional Question Bank

| Module | Completion | Accessed |
|--|--------------------------|------------------|
| How To Use This Question Bank | <input type="checkbox"/> | 01/30/11 4:38 PM |
| Regulatory Agency Governance | <input type="checkbox"/> | 01/30/11 5:26 PM |
| Quality Systems | <input type="checkbox"/> | Not Accessed |
| Laboratory Systems | <input type="checkbox"/> | Not Accessed |
| Infrastructure: Facilities, Utilities, Equipment | <input type="checkbox"/> | Not Accessed |
| Materials and Supply Chain Management | <input type="checkbox"/> | Not Accessed |
| Sterile and Nonsterile Manufacturing Systems | <input type="checkbox"/> | Not Accessed |
| Filling, Packaging and Labeling | <input type="checkbox"/> | Not Accessed |
| Product Development and Technology Transfer | <input type="checkbox"/> | Not Accessed |
| Full Scored Assessment | <input type="checkbox"/> | Not Accessed |

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ASQ's Question Bank (cont'd)

http://asq.outstart.com - Certified Pharmaceutical GMP Professional Question Bank - Microsoft Internet Explorer provided by Coy

Certified Pharmaceutical GMP Professional Question Bank 2 OF 15

Master batch and completed batch records

Home Previous Next

ASQ
The World's Best at Quality

- Sterile and Nonsterile Manufacturing Systems
 - Master batch and completed batch records
 - Required elements, record processing requirements
 - Objectives
 - Questions
 - Production operations
 - In-process controls
 - Dispensing and weighing controls
 - Requirements for critical unit processes
 - Contamination and cross-contamination
 - Reprocessed and reworked materials
 - Sterile and Nonsterile Manufacturing Systems Assessment

Q: The Master Production and Control Records generally will not include:

- Batch size and list of components.
- Drug product name and strength, and dosage form.
- Name of ingredient supplier and their trade name.
- Name and weight of active ingredient per dosage unit.

Check

Tries Remaining: 1

Q: Batch Production and Control Records review for aseptic processing includes:

- Reports of equipment qualification.
- Environmental and personnel monitoring data.
- Supplier qualification reports.
- Statistical Process Control charts

Check

Tries Remaining: 1

Q: Which of the following is expected to be part of the Batch Production and Control Record for aseptic processing?

- In-process data.
- Environmental and personnel monitoring data.
- Output from support systems.

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More Recommended Reference Material

- WHO Quality Assurance of Pharmaceuticals, A Compendium of Guidelines and Related Materials.
- Current Good Manufacturing Practices: Pharmaceutical, Biologics, and Medical Device Regulations and Guidance Documents Concise Reference, Mindy J. Allport-Settle
- The Indispensable Guide to Good Laboratory Practice (GLP) 2ed, Mark Gregory Slomiany
- Pharmaceutical Quality Control Lab Guidebook, Anthony Luttrell, Daniel Far, Robert Kirsch
- ISO19011S-2008 (Guidelines for Management System Auditing).

Things to know and Materials to have with you

- You need copies of FDA regulations, guidances, ICH documents (there's a ton of them, try partnering with someone to print them out)
- You need a good subject index to your references
- Know terminology (glossary handout)
- Know the difference between laws, regulations, and guidances
- Know how to compare measurements to a spec (Know Rounding Rules and significant figures)
- Cleanroom Classes and where they are used (WHO Quality Assurance of Pharmaceuticals is a good reference)
- Summarize comparisons of FDA/EU/Japan, etc (handout)
- Know the sections in the US Pharmacopeia (general chapters vs monographs, etc)
- Before the test, do a check against the Body of Knowledge to make sure you've covered all of the topics in your reading or reference materials.

Handouts

- Body of Knowledge
- This slide presentation
- Summary of FDA vs EU vs Japan vs
(reporting, record retention, Inspection Frequency, Annual Product Review, etc)
- Glossary of Terms (and references where there is information on those subjects)
- Practice test with answers
- Other useful tidbits
- Also sign email sheet and I can send a table of contents and index for many of the references

Practice Test

Handout

1. The Law which governs Drug Manufacture is:

- A. 21CFR210 Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs
- B. Food, Drug, and Cosmetic Act
- C. Public Health Service Act
- D. ICH Q11 Development and Manufacture of Drug Substances

1. The Law which applies to Drug Manufacture
is:

Answer B. Food, Drug, and Cosmetic Act

21CFR210 is a regulation not a law.
ICHQ11 is a guidance, not a law. And
the Public Health Service Act is not the
law that covers Drug Manufacture

Law, Regulation, Guidance: What's the difference?

- Law: Enacted by Congress (examples-Food, Drug, and Cosmetic Act; Modernization Act)
- Regulations: Requirements that implement and/or enforce a law (e.g. 21 CFR210)
- Guidelines and Guidances: Establish Principles and practices that apply to test procedures, manufacturing practices, scientific standards, protocols, labeling and other technical or policy considerations. Recommendations on how to comply with laws and regulations. These are not mandatory (e.g. ICH, FDA Guidances, PIC documents).
- Directives: European Union-They require that member states achieve a certain result but the states have the flexibility on how to implement.

2. What Law amended the Food, Drug, and Cosmetic act to provide requirements for making and reporting manufacturing changes to an approved application and for distributing a drug product made with such changes?

- A. The Food Drug and Cosmetic Act, the Sequel
- B. The Modernization Act
- C. The Public Health Services Act
- D. None of the above

2. What Law amended the Food, Drug, and cosmetic act to to provide requirements for making and reporting manufacturing changes to an approved application and for distributing a drug product made with such changes?

Answer B. The Modernization Act

Guidance for Industry: Changes to an Approved NDA or ANDA

On November 21, 1997, the President signed the Food and Drug Administration Modernization

Act of 1997 (the Modernization Act).³ Section 116 of the Modernization Act amended the the Act

by adding section 506A, which provides requirements for making and reporting manufacturing changes to an approved application and for distributing a drug product made with such changes.

3. In which International Conference on Harmonization document would you find guidance about risk assessment?

A. ICH Q1

B. ICH Q9

C. PI-007

D. 21CFR 314

3. In which International Conference on Harmonization document would you find guidance about risk assessment?

Answer B. ICH Q9

ICH Q9 Quality Risk Management

4. Put these ICH Q9 Risk Management steps in the correct order:

Risk Review
Risk Identification
Risk Reduction
Risk Evaluation

- A. Risk Identification, Risk evaluation, Risk reduction, Risk Review
- B. Risk Review, Risk Identification, Risk reduction, Risk Evaluation
- C. Risk Reduction, Risk Review, risk Identification
- D. Risk Identification, Risk Review, Risk Evaluation, risk reduction

4. Put these ICH Q9 Risk Management steps in the correct order:

Risk Review

Risk Identification

Risk Reduction

Risk Evaluation

Answer A. Risk Identification, Risk evaluation, Risk reduction, Risk Review

See ICH Q9, section 4.

5. For a Parenteral Drug, which of the following might be tested and have acceptance criteria?

- A. Sterility
- B. Endotoxin
- C. Particle matter
- D. A and B only
- E. All of the above

5. For a Parenteral Drug, which of the following might be tested and have acceptance criteria?

E. All of the Above

See ICH Q6A Test Procedures and
Acceptance Criteria for new Drug
Substances and New Drug Products:
Chemical Substances

6. Medical Products imported into, supplied in, or exported from Australia must be listed in the:

- A. Australian Drug Administration Databank (ADAD)
- B. Australian Register of Therapeutic Goods (ARTG)
- C. Drugs Down Under List (DDUL).
- D. Australian-New Zealand Drug Register (ANZDR)

6. Medical Products imported into, supplied in, or exported from Australia must be listed in the:

Answer: B. Australian Register of Therapeutic Goods

Australian Regulation of Prescription Medical Products (Therapeutic Goods Administration)

http://www.tga.gov.au/docs/html/pmeds_reg.htm

7. In an area immediately adjacent to an aseptic operation, settling plates (90mm diameter) were examined by an engineer and found to have particle counts of 1CFU/4 hours. What actions should be taken?

- A. Stop Production and quarantine product
- B. Notify the FDA of a problem
- C. Conduct a risk assessment
- D. No Action is needed

7. Answer: D No action, Counts are OK

See WHO Quality Assurance of
Pharmaceuticals

And FDA Guidance for
Industry: Sterile Drug Products
Produced by Aseptic Processing

Clean Room Facts from Guidance for Industry - Sterile Drug Products

Produced by Aseptic Processing — Current Good Manufacturing Practice

- **Critical Area – Class 100 (ISO 5)** A critical area is one in which the sterilized drug product, containers, and closures are exposed to environmental conditions that must be designed to maintain product sterility (§ 211.42(c)(10)). Activities conducted in such areas include manipulations (e.g., aseptic connections, sterile ingredient additions) of sterile materials prior to and during filling and closing operations.
- FDA recommends that the area immediately adjacent to the aseptic processing line meet, at a minimum, Class 10,000 (ISO 7) standards (see Table 1) under dynamic conditions. Manufacturers can also classify this area as Class 1,000 (ISO 6) or maintain the entire aseptic filling room at Class 100 (ISO 5). An area classified at a Class 100,000 (ISO 8) air cleanliness level is appropriate for less critical activities (e.g., equipment cleaning).

personnel present, equipment in place, and operations ongoing). An adequate aseptic processing facility monitoring program also will assess conformance with specified clean area classifications under dynamic conditions on a routine basis.

The following table summarizes clean area air classifications and recommended action levels of microbiological quality (Ref. 1).

TABLE 1- Air Classifications^a

| Clean Area Classification (0.5 µm particles ft ³) | ISO Designation ^b | ≥ 0.5 µm particles m ³ | Microbiological Active Air Action Levels ^c (cfu/m ³) | Microbiological Settling Plates Action Levels ^{d,e} (diam. 90mm; cfu/4 hours) |
|---|------------------------------|-----------------------------------|---|--|
| 100 | 5 | 3,520 | 1 ^e | 1 ^e |
| 1,000 | 6 | 35,200 | 7 | 3 |
| 10,000 | 7 | 352,000 | 10 | 5 |
| 100,000 | 8 | 3,520,000 | 100 | 50 |

^a All classifications based on data measured in the vicinity of exposed materials/articles during periods of activity.
^b ISO 14644-1 designations provide maximum particle concentration values for cleanrooms in multiple industries. An ISO 5 particle concentration is equal to Class 100 and approximately equals EU Grade A.
^c Values represent recommended levels of environmental quality. You may find it appropriate to establish alternate microbiological action levels due to the nature of the operation or method of analysis.
^d The additional use of settling plates is optional.
^e Samples from Class 100 (ISO 5) environments should normally yield no microbiological contaminants.

Two clean areas are of particular importance to sterile drug product quality: the critical area and the supporting clean areas associated with it.

cleanliness and supplied with air that has passed through filters of the required efficiency.

The various operations of component preparation (such as those involving containers and closures), product preparation, filling and sterilization should be carried out in separate areas within a clean area. These areas are classified into four grades (see section 4.1).

Manufacturing operations are divided here into two categories: first, those where the product is terminally sterilized, and second, those which are conducted aseptically at some or all stages.

Quality control

Samples taken for sterility testing should be representative of the whole of the batch, but should, in particular, include samples taken from parts of the batch considered to be most at risk of contamination, for example:

- for products that have been filled aseptically, samples should include containers filled at the beginning and end of the batch and after any significant interruption of work;
- for products that have been heat sterilized in their final containers, consideration should be given to taking samples from that part of the load that is potentially the coolest.

The sterility of the finished product is ensured by validation of the sterilization cycle in the case of terminally sterilized products, and by "media-fills" for aseptically processed products. Batch processing records and, in the case of aseptic processing, environmental quality records, should be examined in conjunction with the results of the sterility tests. The sterility test procedure should be validated for a given product. Pharmacopoeial methods must be used for the validation and performance of the sterility test.

For injectable products, the water for injection and the intermediate and finished products should be monitored for endotoxins, using an established pharmacopoeial method that has been validated for each type of product. For large-volume infusion solutions, such monitoring of water or intermediates should always be done, in addition to any tests required by an approved monograph for the finished product. When a sample fails a test, the cause of such failure should be investigated and remedial action taken where necessary.

Sanitation

The sanitation of clean areas is particularly important. They should be cleaned frequently and thoroughly in accordance with an approved written

Table 1. Limits for microbiological contamination*

| Grade | Air sample (CFU/m ³) | Settle plates (diameter 90 mm) (CFU/4 hours) | Contact plates (diameter 55 mm) (CFU/plate) | Glove print (5 fingers) (CFU/glove) |
|-------|----------------------------------|--|---|-------------------------------------|
| A | <1 | <1 | <1 | <1 |
| B | 10 | 5 | 5 | 5 |
| C | 100 | 50 | 25 | — |
| D | 200 | 100 | 50 | — |

* These are average values. The grades are defined in section 4.1.

* The airborne particulate classification for the four grades is given in Table 2.

* Individual settle plates may be exposed for less than 4 hours.

emergence of resistant strains of microorganisms. In view of its limited effectiveness, ultraviolet light should not be used as a substitute for chemical disinfection.

3.2 Disinfectants and detergents should be monitored for microbiological contamination; dilutions should be kept in previously cleaned containers and should only be stored for defined periods unless sterilized. Disinfectants and detergents used in grade A and B areas (see section 4.1) should be sterilized before use.

3.3 In order to control the microbiological cleanliness of the various grades in operation, the clean areas should be monitored. Where aseptic operations are performed, monitoring should be frequent and methods such as settle plates, and volumetric air and surface sampling (e.g. swabs and contact plates) should be used. The zones should not be contaminated through the sampling methods used in the operations. The results of monitoring should be considered when batch documentation for release of the finished product is reviewed. Both surfaces and personnel should be monitored after critical operations.

3.4 Levels (limits) of detection of microbiological contamination should be established for alert and action purposes, and for monitoring the trends in air quality in the facility. Limits expressed in colony-forming units (CFU) for the microbiological monitoring of clean areas in operation are given in Table 1. The sampling methods and numerical values included in the table are not intended to represent specifications, but are for information only.

4. Manufacture of sterile preparations

4.1 Clean areas for the manufacture of sterile products are classified according to the required characteristics of the environment. Each manufacturing opera-

WHO Quality Assurance
of Pharmaceuticals
A Comparison of Guidelines

the microbiological and given here. Reference should be made to standards such as the European, United States Pharmacopoeias, or in documents issued by the

European Committee for Standardization and the International Organization for Standardization (ISO).

tate in order to minimize the risks of particulate or microbiological contamination of the product or materials being handled.

In order to meet "in operation" conditions, these areas should be designed to reach certain specified air-cleanliness levels in the "at rest" occupancy state. This latter state is the condition where the installation is complete, and production equipment has been installed and is operating, but no operating personnel are present. The "in operation" state is the condition where the installation is functioning in the defined operating mode and the specified number of personnel are present.

For the manufacture of sterile pharmaceutical preparations, four grades are distinguished here, as follows:

- **Grade A:** The local zone for high-risk operations, e.g. filling and making aseptic connections. Normally such conditions are provided by a laminar-airflow workstation. Laminar-airflow systems should provide a homogeneous air speed of approximately 0.45 m/s ± 20% (guidance value) at the working position.
- **Grade B:** In aseptic preparation and filling, the background environment for the grade A zone.
- **Grades C and D:** Clean areas for carrying out less critical stages in the manufacture of sterile products.

The airborne particulate classification for the four grades is given in Table 2. To obtain air of the required characteristics, methods specified by national authorities should be used. It should be noted that:

In order to reach the B, C and D air grades, the number of air changes should be appropriate for the size of the room and the equipment and personnel present in it. At least 20 air changes per hour are usually required for a room with a good airflow pattern and appropriate high-efficiency particulate air (HEPA) filters.

Table 2. Airborne particulate classification for manufacture of sterile pharmaceutical preparations

| Grade | At rest | | In operation | |
|-------|--|--------|--|-------------|
| | Maximum number of particles permitted/m ³ | | Maximum number of particles permitted/m ³ | |
| | 0.5–5.0µm | >5.0µm | 0.5–5.0µm | >5.0µm |
| A | 3500 | 0 | 3500 | 0 |
| B | 3500 | 0 | 350 000 | 2 000 |
| C | 350 000 | 2 000 | 3 500 000 | 20 000 |
| D | 3 500 000 | 20 000 | Not defined | Not defined |

The different airborne particulate classification systems for clean areas are shown in Table 3.

4.2 The particulate conditions given in Table 2 for the "at rest" state should be achieved in the absence of the operating personnel after a short "clean-up" period of about 15–20 minutes (guidance value), after completion of the operations. The particulate conditions given in Table 2 for grade A "in operation" should be maintained in the zone immediately surrounding the product whenever the product or open container is exposed to the environment. It is accepted that it may not always be possible to demonstrate conformity with particulate standards at the point of fill when filling is in progress, owing to the generation of particles or droplets from the product itself.

4.3 In order to control the particulate cleanliness of the various clean areas during operation, they should be monitored.

4.4 Appropriate alert and action limits should be set for the results of particulate and microbiological monitoring. If these limits are exceeded, the appropriate corrective actions should be taken, as prescribed in the operating procedures.

4.5 The area grades as specified in sections 4.6–4.14 must be selected by the manufacturer on the basis of the nature of the process operations being performed and validation runs (e.g. sterile media fills). The determination of an appropriate process area environment and a time limit should be based on the microbiological contamination (bioburden) found.

Table 3. Comparison of different airborne particulate classification systems for clean areas^a

| WHO (GMP) | United States (209E) | United States (customary) | ISO/TC (209) | EEC (GMP) |
|-----------|----------------------|---------------------------|--------------|-----------|
| Grade A | M 3.5 | Class 100 | ISO 5 | Grade A |
| Grade B | M 3.5 | Class 100 | ISO 5 | Grade B |
| Grade C | M 5.5 | Class 10 000 | ISO 7 | Grade C |
| Grade D | M 6.5 | Class 100 000 | ISO 8 | Grade D |

EEC: European Commission; ISO/TC: International Organization for Standardization Technical Committee.

^a Source: references 1–4.

8. What Pharmaceutical Products are within the scope of the Mutual Recognition Agreement between the US and EU?

- A. Human prescription drugs only
- B. Human prescription and non-prescription drugs, Human Biological products, Veterinary drugs, API
- C. Veterinary immunologicals and human biological products
- D. We do not have a Mutual Recognition Agreement between US and EU

8. Pharmaceutical Products covered in the scope of the MRA between US and EU?

Answer: B

See Section 8, Appendix 3 of MRA for US and EU

<http://www.mac.doc.gov/mra/mra.htm>

- human medicinal products including prescription and non-prescription drugs;
- human biologicals including vaccines, and immunologicals;
- veterinary pharmaceuticals, including prescription and non-prescription drugs, with the exclusion of veterinary immunologicals;
- pre-mixes for the preparation of veterinary medicated feeds (EC), Type A medicated articles for the preparation of veterinary medicated feeds (US);
- intermediate products and active pharmaceutical ingredients or bulk pharmaceuticals(US)/starting materials (EC).

Section 8 Appendix 2 (countries included)

U.S. - EU Mutual Recognition Agreement (MRA) - Microsoft Internet Explorer provided by Covidien / Hazelwood

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United States

In the United States, the regulatory authority is the Food and Drug Administration.

European Community

In the European Community, the regulatory authorities are the following :

Austria: Bundesministerium Fur Arbeit, Gesundheit, und Soziales, Wien

Belgium: Ministère van Sociale Zakem, Volksgezondheid en Leefmilieu /Ministere des Affaires Sociales, Sante Publique et Environnement/ Algemeine Farmaceutische Inspectie, Inspection Generale de la Pharmacie, Bruxelles,Brussel.

Denmark: Laegemiddelstryelsen, (Danish Medicines Agency), Bronshoj

Finland: Laakelaitos/Lakemedelsverket (National Agency for Medicines), Helsinki.

France: Agence du Médicament, Direction de l'inspection et des établissements, Saint Denis. (Human)

Agence Nationale du Médicament Vétérinaire, Fougères (Veterinary)

Germany: Bundesgesundheitsministerium, Bonn.

Paul-Ehrlich Institut, Langen (biologicals only)

Zuständige Behörden der 16 Bundeslander: Bayern, Berlin

Brandenburg, Bremen, Hamburg, Hessen, Niedersachsen, Nordrhein- Westfalen, Rheinland-Pfalz, Mecklenberg-Vorpommern, Saarland, Sachsen, Sachsenanhalt, Schleswg-Holstein, Thuringen.

Greece: Ministry of Health and Welfare, National Drug Organisation (E.O.F.), Athens.

Ireland: Irish Medicines Board, Dublin.

Italy: Ministero della Sanità, Dipartimento Farmaci e Farmacovigilanza, Roma. (Human)

Ministero della Sanità, Dipartimento alimenti e nutrizione e sanità pubblica veterinaria - Div. IX, Roma (Veterinary)

Luxembourg: Direction de la Santé, Division de la Pharmacie et des Médicaments, Luxembourg

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Italy: Ministero della Sanità, Dipartimento Farmaci e Farmacovigilanza, Roma. (Human)
Ministero della Sanità, Dipartimento alimenti e nutrizione e sanità pubblica veterinaria - Div. IX, Roma (Veterinary)
Luxembourg: Direction de la Santé, Division de la Pharmacie et des Médicaments, Luxembourg
The Netherlands: Staatstoezicht op de Volksgezondheid, Inspectie voor de Gezondheidszorg, Rijswijk
Portugal: Instituto da Farmácia e do Medicamento (INFARMED), Lisboa
Spain: Ministerio Sanidad y Consumo, Subdirección. General de Control Farmacéutico, Madrid. (Human)
Ministerio de Agricultura Pesca y Alimentación, Madrid, (Veterinary)
Sweden: Läkemedelsverket (Medical Products Agency), Uppsala.
United Kingdom: Medicines Control Agency, London.
Veterinary Medicines Directorate, Addlestone.
European Union: European Commission, Brussels.
European Agency for the Evaluation of Medicinal Products (EMA), London.

APPENDIX 3

Indicative list of Products covered by the Sectoral Annex

Recognizing that precise definition of medicinal products and drugs are to be found in the legislations referred to above, an indicative list of products covered by the agreement is given below:

- human medicinal products including prescription and non-prescription drugs;
- human biologicals including vaccines, and immunologicals;
- veterinary pharmaceuticals, including prescription and non-prescription drugs, with the exclusion of veterinary immunologicals;
- pre-mixes for the preparation of veterinary medicated feeds (EC), Type A medicated articles for the preparation of veterinary medicated feeds (US);
- intermediate products and active pharmaceutical ingredients or bulk pharmaceuticals(US)/starting materials (EC).

APPENDIX 4

Criteria for Assessing Equivalence for Post- and Pre-Approval

I. Legal/Regulatory authority and structure and procedures providing for post- and pre- approval:

9. Your company discovered that it had shipped a drug which was misidentified. How quickly must you notify the FDA (post marketing)?

- A. Immediately
- B. 3 days
- C. 15 days
- D. None of the above

9. Your company discovered that it had shipped a drug which was misidentified. How quickly must you notify the FDA (post marketing)?

Answer: B 3 days

See 21CFR314.81

NDA--Field alert report. The applicant shall submit information of the following kinds about distributed drug products and articles to the FDA district office that is responsible for the facility involved within 3 working days of receipt by the applicant. The information may be provided by telephone or other rapid communication means, with prompt written followup. The report and its mailing cover should be plainly marked: "NDA--Field Alert Report." (i) Information concerning any incident that causes the drug product or its labeling to be mistaken for, or applied to, another article.

(ii) Information concerning any bacteriological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the drug product to meet the specification established for it in the application.

Reporting

| FDA | EU | Japan | Canada |
|---|---|--|---|
| <p>600.80 Must report adverse experiences in 15 days or less for serious and unexpected experiences, must investigate and report again within 15 days. Persons other than manufacturer submit report within 5 days. The licensed manufacturer shall report each adverse experience not reported under paragraph (c)(1)(i) of this section at quarterly intervals, for 3 years from the date of issuance of the biologics license, and then at annual intervals. The licensed manufacturer shall submit each quarterly report within 30 days of the close of the quarter (the first quarter beginning on the date of issuance of the biologics license) and each annual report within 60 days of the anniversary date of the issuance of the biologics license.</p> <p>600.14 Biologic Product Deviations must be reported in 45 days or less</p> <p>606.171 blood related products. You should report a biological product deviation as soon as possible but you must report at a date not to exceed 45-calendar days from the date you, your agent, or another person who performs a manufacturing, holding, or distribution step under your control, acquire information reasonably suggesting that a reportable event has occurred.</p> <p>610.46, 47, within 3 days of blood, blood products test positive for HIV or Hepatitis C, notify consignee to quarantine material from donor</p> <p>314.81 NDA Field Alerts Post Marketing must send report within 3 days of incident involving misidentification or any significant change in product or multiple failures to meet spec</p> <p>Adverse Events that don't require remedial action: 30 days</p> <p>Food Drug Cosmetic Act: Discontinuing manufacture of a life saving drug requires notification of Secretary 6 months prior.</p> <p>26. 14 MRA request for preapproval inspec= within 15 days acknowledge receipt and within 45 days will sent reports of preapproval inspection</p> | <p>Must report Adverse reaction in 15 days. For less serious, they are reported in the periodic safety update at least every 6 months for 2 yrs, then later the frequency is spread out. Same for veterinary medicinal products</p> <p>Adverse Events that don't require remedial action: 10 days for events, 30 days for near miss (this may be applying to biologics)</p> | <p>Adverse Reaction 15 days for serious and 30 days for less serious</p> | <p>Canada's regulation says the drug manufacturer must have a system (couldn't find any specific requirement)</p> |

Annual Reporting

| FDA Annual Product Review (21CFR211.180) | EC Annual Product Quality Review | ICH Q7A Annual Product Review (API) |
|--|---|--|
| Representative number of batch records | Regular periodic or rolling quality reviews of all licensed medicinal products, including | |
| Review of complaints, recalls, returned or salvaged drug products and investigations conducted under 211.192 (drug production record review) | export only products, should be conducted with the objective of verifying the | Review of all quality related returns, complaints, and recalls |
| investigations of investigations of yield discrepancies, batches or component failure to meet spec,) | consistency of the existing process, the appropriateness of current specifications for | Review of all batches that fail to meet specification, critical deviations or nonconformances and related investigations |
| | both starting materials and finished product to highlight any trends and to identify | Critical to process control and critical API test results |
| | product and process improvements. Such reviews should normally be conducted and | Review of any process Changes or analytical methods |
| | documented annually, taking into account previous reviews, and should include at least: | Review of stability monitoring results |
| | (i) A review of starting materials and packaging materials used for the product, | Review of adequacy of corrective actions |
| | especially those from new sources. | |
| | (ii) A review of critical in-process controls and finished product results. | |
| | (iii) A review of all batches that failed to meet established specification(s) and their | |
| | investigation. | |
| | (iv) A review of all significant deviations or non-conformances, their related | |
| | investigations, and the effectiveness of resultant corrective and preventative | |
| | actions taken. | |
| | (v) A review of all changes carried out to the processes or analytical methods. | |
| | (vi) A review of Marketing Authorisation variations submitted/granted/refused, | |
| | including those for third country (export only) dossiers. | |
| | (vii) A review of the results of the stability monitoring programme and any adverse | |
| | trends. | |
| | (viii) A review of all quality-related returns, complaints and recalls and the | |
| | investigations performed at the time. | |
| | (ix) A review of adequacy of any other previous product process or equipment | |
| | corrective actions. | |
| | (x) For new marketing authorisations and variations to marketing authorisations, a | |
| | review of post-marketing commitments. | |
| | (xi) The qualification status of relevant equipment and utilities, e.g. HVAC, water, | |
| | compressed gases, etc. | |
| | (xii) A review of Technical Agreements to ensure that they are up to date. | |

Annual Reporting

<http://pharmtech.findpharma.com/pharmtech/Peer-Reviewed+Research/Product-AnnualQuality-Review-USndashEU-Comparative/ArticleStandard/Article/detail/500406>

Table I: Review objectives.

| Objectives | FDA: Product Annual Review 21 CFR 211.180(e)* | EC: Product Quality Review (1.5)* | ICH Q7A: Product Quality Review (2.5)* |
|---|--|---|---|
| Determine appropriateness of, and/or need to change, product specifications | Required | Required | Not specified |
| Appropriateness of starting material specifications | Not specified | Required | Not specified |
| Determine the need to change manufacturing procedures | Required | Not specified | Not specified |
| Determine the need to change manufacturing control procedures | Required | Not specified | Not specified |
| Verify consistency of the existing process | Not specified | Required | Required |
| Determine the need to revalidate the production process | Not specified | Required (also specified in EU GMP Annex 15) | Required (also specified in section 12.6) |
| Highlight trends | Expected, not specified | Required | Not specified |
| Identify product and process improvements | Not specified | Required | Not specified |
| Identify corrective actions | Expected, not specified | Required | Required |

*CFR denotes Code of Federal Regulations, EC denotes European Commission; and ICH denotes International Conference on Harmonization.

10. What information is not required to be part of a batch record?

- A. Copy of the master production or control record, checked for accuracy, dated and signed.
- B. Dates of each significant Manufacturing step.
- C. Major equipment and lines used
- D. Sampling performed
- E. Manufacturing operator training records.
- F. All of these are required

10. What information is not required to be part
of a batch record

Answer: E. Manufacturing operator training
records

See 21CFR211.188

<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=211.188>

11. Records of Complaints for a drug product must be maintained. Which of the following best describes retention requirements?

- A. 1 year after the complaint was received.
- B. 1 year after expiry of drug product
- C. Whichever is longer of A or B
- D. 3 years after the last batch was distributed

11. Records of Complaints for a drug product must be maintained. Which of the following best describes retention requirements?

Answer: C whichever is longer of A or B

See 211.198

Record retention

| Record Retention FDA | EU | Japan | WHO |
|---|---|---|--|
| <p>211.180(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.</p> <p>211.180(b) Records shall be maintained for all components, drug product containers, closures, and labeling for at least 1 year after the expiration date 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 last lot of drug product incorporating the component or using the container, closure, or labeling.</p> <p>211.180(c) All records required under this part, or copies of such records, shall be readily available for authorized inspection during the retention period at the establishment where the activities described in such records occurred. These records or copies thereof shall be subject to photocopying or other means of reproduction as part of such inspection. Records that can be immediately retrieved from another location by computer or other electronic means shall be considered as meeting the requirements of this paragraph.</p> <p>211.180(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. Where reduction techniques, such as microfilming, are used, suitable reader and photocopying equipment shall be readily available.</p> <p>211.180(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 in drug product specifications or manufacturing or control procedures. Written procedures shall be established and followed for such evaluations and shall include provisions for:</p> <p>(1) A review of a representative number of batches, whether approved or rejected, and, where applicable, records associated with the batch.</p> <p>(2) A review of complaints, recalls, returned or salvaged drug products, and investigations conducted under 211.192 for each drug product.</p> <p>211.180(f) Procedures shall be established to assure that the responsible officials of the firm, if they are not personally involved in or immediately aware of such actions, are notified in writing of any investigations conducted under 211.198, 211.204, or 211.208 of these regulations, any recalls, reports of inspectional observations issued by the Food and Drug Administration, or any regulatory actions relating to good manufacturing practices brought by the Food and Drug Administration.</p> <p>211.198 drug product complaint records (b) A written record of each complaint shall be maintained in a file designated for drug product complaints. The file regarding such drug product complaints shall be maintained at the establishment where the drug product involved was manufactured, processed, or packed, or such file may be maintained at another facility if the written records in such files are readily available for inspection at that other facility. Written records involving a drug product shall be maintained until at least 1 year after the expiration date of the drug product, or 1 year after the date that the complaint was received, whichever is longer. In the case of certain OTC drug products lacking expiration dating because they meet the criteria for exemption under 211.137, such written records shall be maintained for 3 years after distribution of the drug product.</p> | <p>Medicinal product batch documentation retained 1 year after expiration date of batches or 5 years after certification whichever is longer (directive 2003/94/EC)</p> <p>Eudralex vol 4 part II all production, control, and distribution records should be retained for at least 1 year after expiry date of the batch. For APIs with retest dates, records should be retained for at least 3 years after the batch is completely distributed.</p> <p>records of radio pharmaceuticals SHOULD be retained 3 years (annex)</p> <p>Investigational medicinal product batch documentatoin should be retained for 5 years after completion or formal discontinuation of the last clinical trial in which the batch was used (directive 2003/84/EC)</p> <p>Documents from clinical trials retained for at least 5 years after completion (directive 2005/28/EC)</p> | <p>Safety assurance records, training, in house inspections 5 years</p> <p>Biologic Product Safety Assurance 10 years</p> | <p>Batch Records 1 year beyond expiration of finished product or specified period if no expiry date</p> <p>Lot Processing records for Biological Product 2 years beyond expiry date of lot</p> |

Sample Retention

Sample Retention

| | FDA | EU | ICH |
|------------------------------|--|---|---|
| reserve drug samples 211.170 | <p>a) An appropriately identified reserve sample that is representative of each lot in each shipment of each active ingredient shall be retained. The reserve sample consists of at least twice the quantity necessary for all tests required to determine whether the active ingredient meets its established specifications, except for sterility and pyrogen testing. The retention time is (1) For an active ingredient in a drug product other than those described in paragraphs (a) (2) and (3) of this section, the reserve sample shall be retained for 1 year after the expiration date of the last lot of the drug product containing the active ingredient.</p> <p>(2) For an active ingredient in a radioactive drug product, except for nonradioactive reagent kits, the reserve sample shall be retained for:</p> <p>(i) Three months after the expiration date of the last lot of the drug product containing the active ingredient if the expiration dating period of the drug product is 30 days or less; or</p> <p>(ii) Six months after the expiration date of the last lot of the drug product containing the active ingredient if the expiration dating period of the drug product is more than 30 days.</p> <p>(3) For an active ingredient in an OTC drug product that is exempt from bearing an expiration date under 211.137, the reserve sample shall be retained for 3 years after distribution of the last lot of the drug product containing the active ingredient.</p> <p>(b) An appropriately identified reserve sample that is representative of each lot or batch of drug product shall be retained and stored under conditions consistent with product labeling. The reserve sample shall be stored in the same immediate container-closure system in which the drug product is marketed or in one that has essentially the same characteristics. The reserve sample consists of at least twice the quantity necessary to perform all the required tests, except those for sterility and pyrogens. Except for those for drug products described in paragraph (b)(2) of this section, reserve samples from representative sample lots or batches selected by acceptable statistical procedures shall be examined visually at least once a year for evidence of deterioration unless visual examination would affect the integrity of the reserve sample. Any evidence of reserve sample deterioration shall be investigated in accordance with 211.192. The results of the examination shall be recorded and maintained with other stability data on the drug product. Reserve samples of compressed medical gases need not be retained. The re</p> <p>(1) For a drug product other than those described in paragraphs (b) (2) and (3) of this section, the reserve sample shall be retained for 1 year after the expiration date of the drug product.</p> <p>(2) For a radioactive drug product, except for nonradioactive reagent kits, the reserve sample shall be retained for:</p> <p>(i) Three months after the expiration date of the drug product if the expiration dating period of the drug product is 30 days or less; or</p> <p>(ii) Six months after the expiration date of the drug product if the expiration dating period of the drug product is more than 30 days.</p> <p>(3) For an OTC drug product that is exempt for bearing an expiration date under 211.137, the reserve sample must be retained for 3 years after the lot or batch of drug product is distributed.</p> | <p>Samples from each batch of finished product retained 1 year past expiry date (directive 2003/94/EC)</p> <p>For investigational medicinal products, samples from each batch retained for 2 years after completion or after formal discontinuation of last clinical trial whichever is longer. (directive 2003/94/EC)</p> <p>Samples from starting materials retained 2 years after product release.</p> | <p>ICH Q7H guidance, API reserve sample retained for 1yr past expiry date, or 3years after distribution of the batch which ever is longer. APIs with retest dates, should be retained 3 years</p> |

12. Which of the following is a test commonly used for detecting the presence of endotoxins in parenterals?

- A. Limulous amebocyte lysate test
- B. Refractive index
- C. Infrared absorption
- D. Chromatography
- E. Injection into humans

12. Answer: A. Limulus Amebocyte Lysate test (derived from circulating blood cells from the horseshoe crab and clots in the presence of an endotoxin). Before this test, endotoxins used to be injected into rabbits and their temperatures monitored.



Our friend, Limulus

Polyphemus

13. Which of the following is not a Lyophilization – Critical Process Parameter?

- A. Shelf Temperature
- B. Chamber Pressure
- C. Time
- D. Shelf Life

13. Which is not a Lyophilization Critical Process Parameter

Answer: D Shelf Life

- <http://americanpharmaceuticalreview.com/ViewArticle.aspx?ContentID=343>
- <http://www.lyotechnology.com/aboutus/lyophilization.html>
- * **Lyophilization: Growing with Biotechnology**
<http://www.genengnews.com/gen-articles/lyophilization-growing-with-biotechnology/1083/>
- Steps: Product preparation, freezing (freezing rate is critical, amorphous material must stay amorphous, crystalline material must stay crystalline), primary drying, secondary drying, sterile area
- Lyophilization equipment: drying chamber, cooling system (condensers, etc), vacuum system.
- Suggestion: When you're trying to find information on crystal process parameters, articles as well as information from equipment vendors is a good source.
- ICH Q8 Annex is a good reference for general discussion on the topic of parameters and variables.
- Also think about critical quality attributes (characteristics that need to be within limits to ensure product quality). Examples depending on the particular product: sterility (parenterals), particle size distribution (raw materials),

Fishbone Diagram to identify process parameters (example below is for a tableting process)

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A. Use of a risk assessment tool.

For example, a cross-functional team of experts could work together to develop an Ishikawa (fishbone) diagram that identifies potential variables which can have an impact on the desired quality attribute. The team could then rank the variables based on probability, severity, and detectability using failure mode effects analysis (FMEA) or similar tools based on prior knowledge and initial experimental data. Design of experiments or other experimental approaches could then be used to evaluate the impact of the higher ranked variables, to gain greater understanding of the process, and to develop a proper control strategy.

Ishikawa Diagram

The diagram is a fishbone-style Ishikawa diagram for a tableting process. The main process flow is Tablet, which is influenced by Analytical (Sampling, Method) and Drying (Temp, Ret, Air Flow, Shock Cycle). The Drying process is influenced by Compressing (Precompressing, Main Compressing, Feeder Speed, Press Speed, Punch Penetration, Depth, Tooling, Feed, Frame) and Granulation (Chopper Speed, Mixer Speed, Endpoint, Power, Time). The Compressing process is influenced by Plant Factors (Temp/Rt, Operator, Training). The Granulation process is influenced by Raw Materials (Water, Binder, Temp, Spray Rate, Spray Pattern, P.S., Scrape Down, Lubricant, Disintegrant, Binder) and other factors (Drug Substance, Age, P.S., LOD, Process Conditions, Diluents, P.S., LOD, Other).

Critical Process parameter definition

Critical Process Parameters (CPP): A Process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality. (ICH Q8 (R1)).

How might you identify critical process parameters if you are not familiar with the process?

- Equipment vendor sites often describe process in detail at their websites
- On-line articles about the process

14. The required assay limits are $\geq 98.0\%$ and $\leq 101.5\%$

Which of the following assays meet the requirement?

- A. 97.96% and 98.12%
- B. 98.12% and 101.57%
- C. 97.45% only
- D. 101.61% only
- E. None of the above

14. The required assay limits are $\geq 98\%$ and $\leq 101.5\%$
 Which of the following assays
 meet the requirement? Answer: A

USP



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EPA U.S. Environmental Protection Agency
 FCC Food Chemicals Codex
 FDA U.S. Food and Drug Administration
 HIMA Health Industry Manufacturers Association
 ISO International Organization for Standardization
 IUPAC International Union of Pure and Applied Chemistry
 JP Japanese Pharmacopoeia
 NIST National Institute of Standards and Technology
 USAN United States Adopted Names
 WHO World Health Organization

Abbreviated Statements in Monographs—Incomplete sentences are employed in various portions of the monographs for directness and brevity. Where the limit tests are so abbreviated, it is to be understood that the chapter numbers (shown in angle brackets>) designate the respective procedures to be followed, and that the values specified after the colon are the required limits.

SIGNIFICANT FIGURES AND TOLERANCES

Where limits are expressed numerically herein, the upper and lower limits of a range include the two values themselves and all intermediate values, but no values outside the limits. The limits expressed in monograph definitions and tests, regardless of whether the values are expressed as percentages or as absolute numbers, are considered significant to the last digit shown.

Equivalence Statements in Titrimetric Procedures—The directions for titrimetric procedures conclude with a statement of the weight of the analyte that is equivalent to each mL of the standardized titrant. In such an equivalence statement, it is to be understood that the number of significant figures in the concentration of the titrant corresponds to the number of significant figures in the weight of the analyte. Blank corrections are to be made for all titrimetric assays where appropriate (see *Titrimetry* (541)).

Tolerances—The limits specified in the monographs for Pharmacopoeial articles are established with a view to the use of these articles as drugs, nutritional or dietary supplements, or devices, except where it is indicated otherwise. The use of the molecular formula for the active ingredient(s) named in defining the required strength of a Pharmacopoeial article is intended to designate the chemical entity or entities, as given in the complete chemical name of the article, having absolute (100 percent) purity.

expression by the following procedure. Intermediate calculations (e.g., slope for linearity in *Validation of Compendial Methods* (1225)) may be rounded for reporting purposes, but the original value (not rounded) should be used for any additional required calculations. Rounding off should not be done until the final calculations for the reportable value have been completed. [NOTE—Limits, which are fixed numbers, are not rounded off.]

A reportable value is often a summary value for several individual determinations. It is the end result of a completed measurement method, as documented. It is the value compared with the acceptance criterion. In most cases, the reportable value is used as documentation for internal or external users.

When rounding off is required, consider only one digit in the decimal place to the right of the last place in the limit expression. If this digit is smaller than 5, it is eliminated and the preceding digit is unchanged. If this digit is greater than 5, it is eliminated and the preceding digit is increased by one. If this digit equals 5, the 5 is eliminated and the preceding digit is increased by one.

Illustration of Rounding Numerical Values for Comparison with Requirements

| Compendial Requirement | Unrounded Value | Rounded Result | Conforms |
|----------------------------|-----------------|----------------|----------|
| Assay limit $\geq 98.0\%$ | 97.96% | 98.0% | Yes |
| | 97.92% | 97.9% | No |
| | 97.95% | 98.0% | Yes |
| Assay limit $\leq 101.5\%$ | 101.55% | 101.6% | No |
| | 101.46% | 101.5% | Yes |
| | 101.45% | 101.5% | Yes |
| | 101.45% | 101.5% | Yes |
| Limit test $\leq 0.02\%$ | 0.025% | 0.03% | No |
| | 0.015% | 0.02% | Yes |
| | 0.027% | 0.03% | No |
| Limit test ≤ 3 ppm | 0.00035% | 0.0004% | No |
| | 0.00025% | 0.0003% | Yes |
| | 0.00028% | 0.0003% | Yes |

GENERAL CHAPTERS

Each general chapter is assigned a number that appears in brackets adjacent to the chapter name (e.g., (621) *Chromatography*). Articles recognized in these compendia must comply with the official standards and tests and assays in the General Notices, relevant monographs, and General Chapters numbered below 1000. General Chapters numbered above 1000 are considered interpretive and are intended to provide information on, give definition to, or describe a

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15. The Monograph for Amoxicillin in the US Pharmacopeia lists pH between 3.5 and 6.0 in a solution containing 2mg per ml as determined by general test <791>. Which is a true statement?

- A. The pH range is a requirement but the test is a recommendation.
- B. Both the test <791> and the pH range are requirements.
- C. Neither the test nor the pH range are requirements but just recommendations.
- D. The test <791> is a requirement but the pH is not.

15. Answer: B Both the pH range and the test <791> are required

- General Notices: Contain information on abbreviations, significant figures, units of potency, solubility, containers, storage temperature and humidity, definitions and more that is relevant to the monographs and tests.
- Monographs: Cover identity, strength, quality, and purity of an official article determined by the definition, physical properties, tests, assays, and other specifications related to the article as well as other requirements.
- General Chapters (Tests and Assays): A number in brackets follows the name of the test. Tests with numbers less than 1000 describe general requirements for tests and Assays.
- General Information Chapters (General Chapters with numbers greater than <1000> are interpretive and intended to provide information and description. They don't contain official standards, tests, assays or other mandatory requirements.

16. Which of the following is not one of the 4 elements of a quality system as discussed in ICHQ10?

- A. Corrective/Preventive Action System
- B. Change Management System
- C. 5 S
- D. Process Performance and Product Quality
- E. Management Review

16. Which of the following is not one of the 4 elements of a quality system as defined in

ICHQ10? Answer: C 5S

See ICH10

17. A single batch has been found to be outside the spec. What should happen first?

- A. Stop shipment of all product.
- B. Analyst and supervisor, verify the accuracy of the measurement.
- C. Analyst remeasures the material 10 times. It passes once, so the operator records the passing result.
- D. Quality Control conducts a full scale investigation including other possibly affected departments.
- E. Supervisor shuts down the production line.

17. A single batch has been found to be outside the spec. What should happen first?

Answer B. Analyst and supervisor, verify the accuracy of the measurement.

Out of specification (A good Reference is Pharmaceutical Quality Control Lab Guidebook (A. Luttrell, et al)

- OOT (out of Trend); OOS (out of Specification)
- A single OOS, requires investigation by laboratory personell and supervisor. Investigation preserved in investigation report which includes conclusion and follow-up. Other batches that could be involved must also be investigated. (see also **21CFR 211.192**)
- Phase I (Laboratory investigation of OOS): Involves Analyst and supervisor. Includes first check accuracy of the laboratory measurement, if no measurement error, then a full scale investigation should be done and documented led by Quality Control Unit-(**See FDA Guidance for Investigating OOS**)
- Phase II (Full Scale investigation of OOS): Conducted by Quality Control unit and Involves all departments that could be implicated; Includes review of sampling and production records, additional laboratory testing, investigating other batches, identifying root cause, taking corrective and preventive actions; written record signed by production and quality control unit personnel.- (See FDA Guidance for Investigating OOS)
- Testing to compliance is not OK (i.e. retesting until you get a “Pass”).
- Averaging to compensate for measurement variability might be OK but not just so that the average passes (even though some of the measurements do not). Hard to justify unless the normal measurement method involves averaging multiple measurements.
- See **ICHQ7A** for Guidance on OOS investigation of APIs

18. All of these items are included in a Master production and control record:

- *Name and strength of the product and a description of the dosage form.*
- *Name and weight or measure of each active ingredient per dosage unit.*
- *List components designated by names or codes*
- *A statement of theoretical yield*
- *A statement of theoretical weight or measure at appropriate phases of processing.*

A. True

B. False

18. All of these items are included in a Master production and control record:

Answer: A. True

See 21CFR 211.186

19. How frequently might a drug firm expect an FDA inspections and name 2 systems which could be inspected?

- A. Biennial inspection with Packaging/labeling and Facilities/Equipment inspected
- B. Biennial inspection with Quality Systems and Laboratory Control inspected
- C. Annual inspection of Facilities/Equipment, Quality Systems, and Packaging/Labeling mandatory
- D. One of the 6 systems per year

19. How frequently might a drug firm expect an FDA inspections and name 2 systems which could be inspected?

Answer: B

FDA Manufacturing Inspections - biennial audit of 2 or more systems- Quality systems is mandatory - The 6 systems are Quality Systems, Facilities/equipment, materials, production, Packaging/Labeling, Laboratory Control (FDA Compliance Program Guidance Manual 7356.002)

Inspection Frequency

FDA

EU

WHO

| FDA | EU | WHO |
|--|---|--|
| 600.20-600.22 Biologics Inspection frequency every 2 years, by FDA | Good clinical practice inspections take place: before during or after the conduct of clinical trials, as part of the verification of applications for marketing authorization, and as a followup for granting authorisation (directive 2005/28/EC) | Premises inspected every 12 to 18 months |
| CGMP inspection of biological drug product biennial (FDA 7345.845) | According to directive 2001/83/EC, 2001/82/EC and 2001/20/EC, respectively, the Competent Authority shall ensure, by means of repeated inspections, and if necessary unannounced inspections, that the legal requirements governing medicinal products are complied with. The Competent Authority may also carry out unannounced inspections at the premises of manufacturers of active substances used as starting materials, or at the premises of marketing authorisation holders whenever it considers that there are grounds for suspecting noncompliance with the principles and guidelines of good manufacturing practice. | Drug manufacturers new drug applicants every 2 years |
| FDA Manufacturing Inspections - biennial audit of 2 or more systems- Quality systems is mandatory - The 6 systems are Quality Systems, Facilities/equipment, materials, production, Packaging/Labeling, Laboratory Control (FDA Compliance Program Guidance Manual 7356.002 | Checks on the persons authorized to engage in the activity of wholesaler in medicinal products and the inspection of their premises, shall be carried out under the responsibility of the Member State which granted the authorization. (2001L0083 —EN —26.01.2007 — 004.001) | |
| API: District office is responsible for determining frequency and depth of coverage of inspections. ..the goal that each API firm will receive biennial inspection coverage....2 systems one of them being Quality systems. (FDA 7356.002F FDA Compliance Program Guidance Manual) | (European Directorate for the quality of Medicinal Products) may ask the Commission or the Agency to request such an inspection when the starting material concerned is the subject of a European Pharmacopoeia monograph. (2001L0083 —EN —26.01.2007 — 004.001) | |
| Drug manufacturers and distributors should conduct an annual inventory of all drug samples | Each Competent Authority should have a written procedure that covers the preparation, realization and supervision of an annual inspection programme. This programme should ensure that the extent and frequency of inspections can be adhered to as planned. Sufficient resources must be determined and made available to ensure that the designated programme of inspections can be carried out in an appropriate manner. EMEA/INS/GMP/354403/2007 Guidance | |
| Secretary performs biweekly screen of AdverseEvent Reporting database | | |

FDA Inspection Operations Manual (Section 5)

- Pre-announced FDA Inspections (types: Pre-market inspections, foreign inspections, Quality Systems/GMP (biennial, initial) Inspections; Eligibility: Non violative history or voluntary corrections, history of having people and documents identified and available)
- Comprehensive Inspection- directs coverage to everything in the firm subject to FDA jurisdiction to determine the firm's compliance status
- Directed Inspection-directs coverage to specific areas to the depth described in the program, assignment , or instructed by supervisor.

Inspection of Biological Products

FDA Guidance Manual 7345.848, Ch 45 (types of inspections)

- Prelicense Inspections
- Level 1 CGMP (all 3 critical elements in each of the 6 systems)
- Level 2 CGMP (3 critical elements in 2 of the systems....one system must be Quality Systems)

The 6 systems (Quality System, Facilities and Equipment System, Materials System, Production System, Packaging and Labeling System, Laboratory Control System)

The 3 critical elements (Standard Operating Procedures, Training, Records)

Inspection of Drug Manufacturing FDA Guidance Manual 7356.002

- Biennial Inspections
- Full Inspection (little is known about the firm, new firm, doubt about compliance, followup from previous regulatory actions. Usually covers at least 4 of the 6 systems, one of which must be the Quality System)
- Abbreviated Inspection (Firm in satisfactory compliance status, no significant recall or alert incidents, little shift in the manufacturing profiles of the firm within the previous to years. Includes at least 2 of the 6 systems, one of which must be the Quality System.)
- The 6 systems (Quality System, Facilities and Equipment System, Materials System, Production System, Packaging and Labeling System, Laboratory Control System)

20. A piece of equipment is being installed.
Select the correct order of the stages

- A. Installation Qualification, performance qualification, and operational qualification.
- B. Performance qualification, operational qualification, validation
- C. Installation Qualification, operational qualification, performance qualification.
- D. Operational qualification, validation only

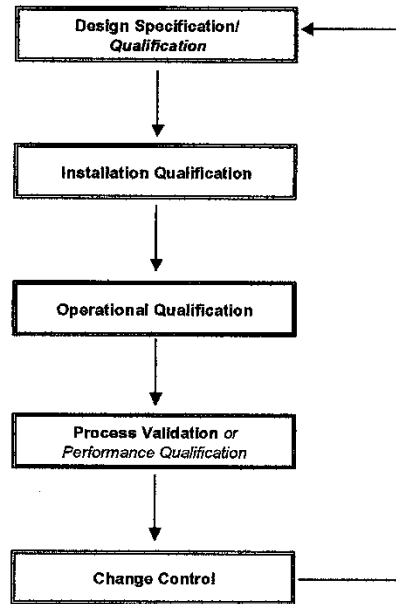
20. A piece of equipment is being installed. Select the correct order of the stages

Answer: C

See PIC/S Recommendations on Validation Master Plan, Installation and Operational Qualification, Non-Sterile Process Validation, Cleaning Validation, section 3. (PI-006-2)

- 2.7.2 While the GMP Guide specifically identifies the responsibility of the Production and Quality Control departments, in practice, other departments, like Engineering and Research and Development as well as Contractors are usually involved in the programme.
- 2.7.3 It is the responsibility of the pharmaceutical company to define the respective responsibilities of its personnel and of external contractors in the qualification and validation programme. This should form part of the Validation Master Plan. However, the Quality Assurance function of a company should normally have a critical role in overseeing the whole qualification and validation process.
- 2.7.4 It is recommended that the validation programme be actively co-ordinated and managed by the company. To this end, validation teams are often formed with specific roles identified and assigned to individual team members. It is imperative that the most senior level of management within the company understands the personnel, time and financial resources required to execute a qualification and validation programme and commits the necessary resources to the work.

3. INTERRELATIONSHIP BETWEEN QUALIFICATION AND VALIDATION



PIC/S Recommendation on Validation Master Plan

21. Which of the following concerning labeling of finished drug products are required by regulation?

- A. For hand applied cut labeling, there must be 100% verification of the correct label and a 2nd person must verify.
- B. Labels of good product must be green for “Go”.
- C. Labels for different strengths of product must be stored separately.
- D. There must be, without exception, procedures covering reconciling the quantity of labels.
- E. A and C are true.

21. Which of the following concerning labeling of finished drug products are required by regulation?

Answer E. See 21CFR211 (sections 211.122 and 211.125). Both A and C are true statements. D is also sometimes true but there is an exception for cut or roll labels which are 100% visually inspected.

22. Over the Counter Drugs (OTC) require Tamper-evident packaging. True or False

A. True

B. False

22. Over the Counter Drugs (OTC) require Tamper-evident packaging. True or False

True

Tamper Evident Packaging is required for OTC exceptions: dermatological, dentifrice, insulin or losenze product
(21CFR 211, sec 211.132)

23. What ISO standard might be beneficial to the pharmaceutical industry which covers the requirements for competence of testing and calibration laboratories?

- A. ISO 19011S
- B. ISO 17025
- C. ISO 15489-1
- D. ISO 9001
- E. ISO 13485

23. What ISO standard might be beneficial to the pharmaceutical industry which covers the requirements for competence of testing and calibration laboratories?

Answer B. ISO17025

24. Typical storage conditions during a long term stability test of a drug substance intended for storage in a refrigerator are:

- A. 12 months, -20 C +/- 5C
- B. 12 months, 5 C +/- 3C
- C. 6 months, 5 C +/- 3C
- D. 8.6 months, 60 F

24. Typical storage conditions during a long term stability test of a drug substance intended for storage in a refrigerator are:

Answer: B 5C +/- 3C, 12 months
ICH Q1A (R2) Stability Testing of New
Drug Substances and Products

7. Storage Conditions (2.1.7) Drug Substance

In general, a drug substance should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and, if applicable, its sensitivity to moisture. The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment, and subsequent use.

The long-term testing should cover a minimum of 12 months' duration on at least three primary batches at the time of submission and should be continued for a period of time sufficient to cover the proposed retest period. Additional data accumulated during the assessment period of the registration application should be submitted to the authorities if requested. Data from the accelerated storage condition and, if appropriate, from the intermediate storage condition can be used to evaluate the effect of short-term excursions outside the label storage conditions (such as might occur during shipping).

Long-term, accelerated, and, where appropriate, intermediate storage conditions for drug substances are detailed in the sections below. The general case should apply if the drug substance is not specifically covered by a subsequent section. Alternative storage conditions can be used if justified.

a. General case (2.1.7.1)

| Study | Storage condition | Minimum time period covered by data at submission |
|----------------|---------------------------------|---|
| Long-term* | 25°C ± 2°C/60% RH ± 5% RH | 12 months |
| | or 30°C ± 2°C/65% RH ± 5% RH | |
| Intermediate** | 30°C ± 2°C/65% RH ± 5% RH | 6 months |
| Accelerated | 40°C ± 2°C/75% RH ± 5% RH | 6 months |

* It is up to the applicant to decide whether long-term stability studies are performed at 25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH.

** If 30°C ± 2°C/65% RH ± 5% RH is the long-term condition, there is no intermediate condition.

If long-term studies are conducted at 25°C ± 2°C/60% RH ± 5% RH and significant change occurs at any time during 6 months' testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria. Testing at the intermediate storage condition should include all tests, unless otherwise justified. The initial application should include a minimum of 6 months' data from a 12-month study at the intermediate storage condition.

Significant change for a drug substance is defined as failure to meet its specification.

b. Drug substances intended for storage in a refrigerator (2.1.7.2)

| Study | Storage condition | Minimum time period covered by data at submission |
|-------------|---------------------------|---|
| Long-term | 5°C ± 3°C | 12 months |
| Accelerated | 25°C ± 2°C/60% RH ± 5% RH | 6 months |

Data from refrigerated storage should be assessed according to the evaluation section of this guidance, except where explicitly noted below.

If significant change occurs between 3 and 6 months' testing at the accelerated storage condition, the proposed retest period should be based on the real time data available at the long-term storage condition.

If significant change occurs within the first 3 months' testing at the accelerated storage condition, a discussion should be provided to address the effect of short-term excursions outside the label storage condition (e.g., during shipping or handling). This discussion can be supported, if appropriate, by further testing on a single batch of the drug substance for a period shorter than 3 months but with more frequent testing than usual. It is considered unnecessary to continue to test a drug substance through 6 months when a significant change has occurred within the first 3 months.

c. Drug substances intended for storage in a freezer (2.1.7.3)

| Study | Storage condition | Minimum time period covered by data at submission |
|-----------|-------------------|---|
| Long-term | -20°C ± 5°C | 12 months |

tested for antimicrobial preservative effectiveness (in addition to preservative content) at the proposed shelf life for verification purposes, regardless of whether there is a difference between the release and shelf life acceptance criteria for preservative content.

6. Testing Frequency (2.2.6)

For long-term studies, frequency of testing should be sufficient to establish the stability profile of the drug product. For products with a proposed shelf life of at least 12 months, the frequency of testing at the long-term storage condition should normally be every 3 months over the first year, every 6 months over the second year, and annually thereafter through the proposed shelf life.

At the accelerated storage condition, a minimum of three time points, including the initial and final time points (e.g., 0, 3, and 6 months), from a 6-month study is recommended. Where an expectation (based on development experience) exists that results from accelerated testing are likely to approach significant change criteria, increased testing should be conducted either by adding samples at the final time point or by including a fourth time point in the study design.

3 time points

When testing at the intermediate storage condition is called for as a result of significant change at the accelerated storage condition, a minimum of four time points, including the initial and final time points (e.g., 0, 6, 9, 12 months), from a 12-month study is recommended.

Reduced designs (i.e., matrixing or bracketing), where the testing frequency is reduced or certain factor combinations are not tested at all, can be applied if justified.

7. Storage Conditions (2.2.7)

In general, a drug product should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and, if applicable, its sensitivity to moisture or potential for solvent loss. The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment, and subsequent use.

Stability testing of the drug product after constitution or dilution, if applicable, should be conducted to provide information for the labeling on the preparation, storage condition, and in-use period of the constituted or diluted product. This testing should be performed on the constituted or diluted product through the proposed in-use period on primary batches as part of the formal stability studies at initial and final time points, and if full shelf life, long-term data will not be available before submission, at 12 months or the last time point for which data will be available. In general, this testing need not be repeated on commitment batches.

The long-term testing should cover a minimum of 12 months' duration on at least three primary batches at the time of submission and should be continued for a period of time sufficient to cover the proposed shelf life. Additional data accumulated during the assessment period of the registration application should be submitted to the authorities if requested. Data from the accelerated storage condition and, if appropriate, from the intermediate storage condition can be used to evaluate the effect of short-term excursions outside the label storage conditions (such as might occur during shipping).

Long-term, accelerated, and, where appropriate, intermediate storage conditions for drug products are detailed in the sections below. The general case should apply if the drug product is not specifically covered by a subsequent section. Alternative storage conditions can be used if justified.

a. General case (2.2.7.1)

| Study | Storage condition | Minimum time period covered by data at submission |
|----------------|--|---|
| Long-term* | 25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH | 12 months |
| Intermediate** | 30°C ± 2°C/65% RH ± 5% RH | 6 months |
| Accelerated | 40°C ± 2°C/75% RH ± 5% RH | 6 months |

Send all for drug stability

* It is up to the applicant to decide whether long-term stability studies are performed at 25°C ± 2°C/60% RH ± 5% RH or 30°C ± 2°C/65% RH ± 5% RH.

** If 30°C ± 2°C/65% RH ± 5% RH is the long-term condition, there is no intermediate condition.

If long-term studies are conducted at 25°C ± 2°C/60% RH ± 5% RH and significant change occurs at any time during 6 months' testing at the accelerated storage condition, additional testing at the intermediate storage condition should be conducted and evaluated against significant change criteria. The initial application should include a minimum of 6 months' data from a 12-month study at the intermediate storage condition.

Significant Change

In general, significant change for a drug product is defined as one or more of the following (as appropriate for the dosage form):

- A 5 percent change in assay from its initial value, or failure to meet the acceptance criteria for potency when using biological or immunological procedures
- Any degradation product's exceeding its acceptance criterion
- Failure to meet the acceptance criteria for appearance, physical attributes, and functionality test (e.g., color, phase separation, resuspendibility, caking, hardness, dose delivery per actuation). However, some changes in physical attributes (e.g., softening of suppositories, melting of creams) may be expected under accelerated conditions.
- Failure to meet the acceptance criterion for pH
- Failure to meet the acceptance criteria for dissolution for 12 dosage units

b. Drug products packaged in impermeable containers (2.2.7.2)

Sensitivity to moisture or potential for solvent loss is not a concern for drug products packaged in impermeable containers that provide a permanent barrier to passage of moisture or solvent. Thus, stability studies for products stored in impermeable containers can be conducted under any controlled or ambient humidity condition.

c. Drug products packaged in semipermeable containers (2.2.7.3)

Aqueous-based products packaged in semipermeable containers should be evaluated for potential water loss in addition to physical, chemical, biological, and microbiological stability. This evaluation can be carried out under conditions of low relative humidity, as discussed below. Ultimately, it should be demonstrated that aqueous-based drug products stored in semipermeable containers can withstand low relative humidity environments. Other comparable approaches can be developed and reported for nonaqueous, solvent-based products.

| Study | Storage condition | Minimum time period covered by data at submission |
|----------------|--|---|
| Long-term * | 25°C ± 2°C/40% RH ± 5% RH or 30°C ± 2°C/35% RH ± 5% RH | 12 months |
| Intermediate** | 30°C ± 2°C/65% RH ± 5% RH | 6 months |
| Accelerated | 40°C ± 2°C/not more than (NMT) 25% RH | 6 months |

* It is up to the applicant to decide whether long-term stability studies are performed at 25°C ± 2°C/40% RH ± 5% RH or 30°C ± 2°C/35% RH ± 5% RH.

** If 30°C ± 2°C/35% RH ± 5% RH is the long-term condition, there is no intermediate condition.

When long-term studies are conducted at 25°C ± 2°C/40% RH ± 5% RH and significant change other than water loss occurs during the 6 months' testing at the accelerated storage condition, additional testing at the intermediate storage condition should be performed, as described under the general case, to evaluate the temperature effect at 30°C. A significant change in water loss alone at the accelerated storage condition does not necessitate testing at the intermediate storage condition. However, data should be provided to demonstrate that the drug product will not have significant water loss throughout the proposed shelf life if stored at 25°C and the reference relative humidity of 40 percent RH.

Significant Change →

A 5 percent loss in water from its initial value is considered a significant change for a product packaged in a semipermeable container after an equivalent of 3 months' storage at 40°C/NMT 25 percent RH. However, for small containers (1 mL or less) or unit-dose products, a water loss of 5 percent or more after an equivalent of 3 months' storage at 40°C/NMT 25 percent RH may be appropriate if justified.

An alternative approach to studying at the reference relative humidity as recommended in the table above (for either long-term or accelerated testing) is performing the stability studies under higher relative humidity and deriving the water loss at the reference relative humidity through calculation. This can be achieved by experimentally determining the permeation coefficient for the container closure system or, as shown in the example below, using the calculated ratio of water loss rates between the two humidity conditions at the same temperature. The permeation coefficient for a container closure system can be experimentally determined by using the worst case scenario (e.g., the most diluted of a series of concentrations) for the proposed drug product.

Example of an approach for determining water loss:

For a product in a given container closure system, container size, and fill, an appropriate approach for deriving the water loss rate at the reference relative humidity is to multiply the water loss rate measured at an alternative relative

humidity at the same temperature by a water loss rate ratio shown in the table below. A linear water loss rate at the alternative relative humidity over the storage period should be demonstrated. For example, at a given temperature (e.g., 40°C), the calculated water loss rate during storage at NMT 25 percent RH is the water loss rate measured at 75 percent RH multiplied by 3.0, the corresponding water loss rate ratio.

| Alternative relative humidity | Reference relative humidity | Ratio of water loss rates at a given temperature |
|-------------------------------|-----------------------------|--|
| 60% RH | 25% RH | 1.9 |
| 60% RH | 40% RH | 1.5 |
| 65% RH | 35% RH | 1.9 |
| 75% RH | 25% RH | 3.0 |

Valid water loss rate ratios at relative humidity conditions other than those shown in the table above can also be used.

d. Drug products intended for storage in a refrigerator (2.2.7.4)

| Study | Storage condition | Minimum time period covered by data at submission |
|-------------|---------------------------|---|
| Long-term | 5°C ± 3°C | 12 months |
| Accelerated | 25°C ± 2°C/60% RH ± 5% RH | 6 months |

If the drug product is packaged in a semipermeable container, appropriate information should be provided to assess the extent of water loss.

Data from refrigerated storage should be assessed according to the evaluation section of this guidance, except where explicitly noted below.

If significant change occurs between 3 and 6 months' testing at the accelerated storage condition, the proposed shelf life should be based on the real time data available from the long-term storage condition.

If significant change occurs within the first 3 months' testing at the accelerated storage condition, a discussion should be provided to address the effect of short-term excursions outside the label storage condition (e.g., during shipment and handling). This discussion can be supported, if appropriate, by further testing on a single batch of the drug product for a period shorter than 3 months but with more frequent testing than usual. It is considered unnecessary to continue to test a product through 6 months when a significant change has occurred within the first 3 months.

e. Drug products intended for storage in a freezer (2.2.7.5)

| Study | Storage condition | Minimum time period covered by data at submission |
|-----------|-------------------|---|
| Long-term | -20°C ± 5°C | 12 months |

For drug products intended for storage in a freezer, the shelf life should be based on the real time data obtained at the long-term storage condition. In the absence of an accelerated storage condition for drug products intended to be stored in a freezer, testing on a single batch at an elevated temperature (e.g., 5°C ± 3°C or 25°C ± 2°C) for an appropriate time period should be conducted to address the effect of short-term excursions outside the proposed label storage condition.

f. Drug products intended for storage below -20°C (2.2.7.6)

Drug products intended for storage below -20°C should be treated on a case-by-case basis.

8. Stability Commitment (2.2.8)

When available long-term stability data on primary batches do not cover the proposed shelf life granted at the time of approval, a commitment should be made to continue the stability studies postapproval to firmly establish the shelf life.

Where the submission includes long-term stability data from three production batches covering the proposed shelf life, a postapproval commitment is considered unnecessary. Otherwise, one of the following commitments should be made:

25. What are some of the enforcement actions available for violations at a Biologic facility?

- A. Warning Letter
- B. License Revocation
- C. Injunction
- D. License Suspension
- E. All of the above

25. What are some of the enforcement actions available for violations at a Biologic facility?

Answer: E. All of the above
Inspection of Biological Drug
Products 7345.848 Ch 45

Inspection of Biological Drug Products 7345.848 Ch 45

23

immediate action is indicated, e.g., license suspension, a temporary restraining order (TRO), etc. See RPM Chapter 6 regarding an injunction to protect the public health.

When inspectional findings indicate the potential for fraud, e.g., falsification, counterfeiting, illegal importation, and/or drug diversion, the investigator should notify the Team Biologics Compliance Officer, the Team Biologics Core Team Leader, and OCBQ/DCM (HFM-610), who will alert the appropriate OCI office. The investigator should continue to pursue any public health concerns, in coordination with CBER/OCBQ, concurrently.

An initial decision on the type of action to recommend should be consistent with the RPM and be based on the seriousness and frequency of the deficiencies as well as the firm's overall compliance history. For example, classify an inspection report that documents one or more systems **not** in a state-of-control as OAI, and consider recommending a Warning Letter or taking other appropriate action.

For a licensed biologic, the advisory, administrative, and judicial options available include:

| Action | Among other things, consider if, |
|--------------------------------------|--|
| Warning Letter: | Violations of regulatory significance that cause one or more systems to be considered not in a state-of-control. |
| License Revocation (21 CFR 601.5) | <p><u>Notice of Intent to Revoke with Opportunity for Correction:</u> Unable to gain access to the manufacturing facility for inspection Licensed products are not safe or effective for their intended use, or are misbranded with respect to any such use. Manufacturer fails to report a change in accordance with 21 CFR 601.12 Manufacturer fails to conform to applicable standards to ensure product safety, potency and purity Licensed products are no longer manufactured</p> <p><u>Direct Revocation without Opportunity for Correction:</u> Demonstration of willful disregard in addition to above.</p> |
| License Suspension (21 CFR 601.6) | Reasonable grounds for revocation and a danger to health exist. It provides immediate withdrawal of the authorization to ship a biological product in interstate commerce. |
| Seizure | Manufacturer is unwilling or unable to retrieve violative products, or products held for sale are unsuitable for safe use. U.S. Marshal takes possession of products through Court Order pursuant to Section 304 of the Federal Food, Drug, and Cosmetic Act. |
| Injunction | A current health hazard exists, the establishment has a history of uncorrected violations despite previous warnings, suspension of the firm's license would result in an unacceptable shortage of products, and/or to halt intrastate distribution of products manufactured under violative conditions |
| Prosecution | Fraud, gross, flagrant or intentional violations, health hazards, or serious violations that have not been corrected. |

Forms associated with FDA Inspections – FDA Investigations Operations Manual Chapter 5

- Form 482 Written Notice of Inspection
- Form 482a Demand for Records
- Form 483 Inspectional Observations (objectionable conditions).
- Form 484 Receipt for samples
- Inspection Warrant (if refused entry)

26. Which of the following is/are **NOT** required on the label of a Biological Product Container?

- A. Proper name of the product
- B. The poison control center phone number
- C. Lot number or other lot identification
- D. Name, address, and license number of manufacturer
- E. None of the above are required

26. Which of the following is/are **NOT** required on the label of a Biological Product Container (unless the container can't accommodate a label or can only accommodate a partial label?)

Answer: B Poison Control Phone
Number

Requirements for container labeling
can be found in 21CFR610.60

Package labeling in 21CFR610.61,
21CFR610.62

Caution!

- Be observant for questions that say what is “NOT” included and All are true “except”. It is easy during a test to not notices the “Not” and the “Except” and answer incorrectly.

27. Mammalian protein can not be used in the production of animal feed. (True or False)

A. True

B. False

C. None of the above

D. All of the above

27. Mammalian protein can not be used in the production of animal feed. (True or False)

A. True

Info on Bovine Spongiform Encephalopathy

Guidance for Industry: Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products

<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm074089.htm>

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| Background Information |
| Federal Register Notices on BSE and Animal Feed Regulation |
| Ruminant Feed Inspections |

Bovine Spongiform Encephalopathy

Bovine Spongiform Encephalopathy (BSE) and Creutzfeldt-Jakob Disease (CJD) belong to the unusual group of progressively degenerative neurological diseases known as transmissible spongiform encephalopathies (TSEs). TSE diseases are characterized by long incubation periods ranging from several months for transmissible mink encephalopathy, to several years for BSE. During the incubation period there is no visible indication of the disease.

FDA has published two rules to protect animals and consumers against BSE by prohibiting the use of most mammalian protein in the manufacture of animal feeds given to ruminant animals and by removing high-risk materials from all animal feed. These rules were published in 1997 and 2008.

In 1997, FDA published a final regulation designed to prevent the spread of BSE through animal feed. The 1997 rule prohibits the use of most mammalian protein in the manufacture of animal feeds given to ruminant animals, such as cows, sheep, and goats. The regulation also requires process and control systems to ensure that feed for ruminants does not contain the prohibited mammalian tissue. The two cases of BSE detected in U.S. cattle were both born before the 1997 feed ban.

In 2008, FDA published a regulation that strengthened the 1997 rule by prohibiting the tissues that have the highest risk for carrying the agent thought to cause BSE in animal feed. These high risk cattle materials are the brains and spinal cords from cattle 30 months of age and older. The 2008 rule also prohibits the use of entire carcass of cattle not inspected and passed for human consumption, unless the cattle are less than 30 months of age, or the brains and spinal cords have been removed.

Please direct questions on CVM's BSE activities to:

Division of Compliance (HFV-230)
Office of Surveillance and Compliance
Center for Veterinary Medicine
U.S. Food and Drug Administration
MPN IV Bldg., Room 146
7519 Standish Place

Pet Safety

- BSE and the Safety of Pets

- Resources for You**
- Bovine Spongiform Encephalopathy (BSE)
 - Bovine Spongiform Encephalopathy (BSE)
 - BSE (Bovine Spongiform Encephalopathy, or Mad Cow Disease) (Centers for Disease Control and Prevention)
 - Bovine Spongiform Encephalopathy (BSE) (U.S. Department of Agriculture)
 - Publicaciones en Español del Centro de Medicina Veterinaria (CVM)

28. What are the 3 Components of a CAPA System as defined in FDA Guidance?

- A. Root cause analysis, corrective action, preventive action.
- B. Containment, root cause analysis, corrective action
- C. Containment, corrective action, preventive action.
- D. Statement of Problem, corrective action, preventive action.

28. What are the 3 Components of a CAPA System as defined in FDA Guidance?

Answer: A Root cause analysis, corrective action, preventive action.

See FDA Guidance for Industry- Quality System Approach to Pharmaceutical CGMP Regulation

Ford 8D Problem Solving Approach for CAPA (in CQA Primer IX-35)

- Form Team
- Define Problem (observed issue, who, what, when, where, why, how, how many, Is/Is not)
- Containment Plan (Short Term Fix).
- Define Root Causes (occurrence and escape)
- Develop Corrective Actions for both occurrence and escape root cause.
- Implement Corrective Actions
- Develop Preventive Actions to prevent reoccurrence
- Recognize Team

29. Company X has an internal electronic documentation system which is used for managing, creation, access, approvals, versioning, electronic signature, etc for their standard operating procedures. Which of the following best describes requirements associated with that system?

- A. Audit trails must be maintained for changes to the documents
- B. Checks are required to ensure that only authorized individual may electronically sign.
- C. Controls so that persons who electronically sign or manage the system have appropriate education or training.
- D. Validation of the System
- E. All of the above

29. Company X has an internal electronic documentation system which is used for managing, creation, access, approvals, versioning, electronic signature, etc for their documents. Which of the following best describes requirements associated with that system?

Answer E: All of the above
See 21CFR11.10

30. What source might you use to learn about the content of a Site Master File?

- A. 21CFR211
- B. Eudralex Vol 4
- C. ICH Q9
- D. ICH Q10
- E. PIC/S PE-008-4 Annex

30. What source might you use to learn about the content of a Site Master File?

Answer: E. PIC/S PE-008-4
Annex

Contents of Site Master File

- 1. General Information on Manufacturer (Contact info, Authorized activities, non-pharmaceutical activities)
- 2. Quality Management System (description, Release procedure of finished goods, management of suppliers and contractors, Quality Risk Management, Product Quality Review methodology)
- 3. Personnel (org chart, number of employees engaged in quality management, production, quality control, storage and distribution)
- 4. Premises and Equipment (description of site, buildings, layouts, HVAC, Water, major equipment, cleaning/sanitation, computer systems (GMP))
- 5. Documentation (description of documentation system and any offsite storage)
- 6. Production (types of products, process validation, material management and warehousing, handling rejected materials)
- 7. Quality Control Activities (physical, chemical, microbiological testing)
- 8. Distribution, complaints, recalls, product defects (types of companies to which product is shipped, systems to ensure correct environmental conditions, system to ensure it goes to correct customer, traceability of product, methods to ensure that product doesn't fall into illegal chain, complaints)
- 9. Self inspections (description of self inspection system, selection of areas to inspect)
- Appendices (manufacturing authorization, dosage forms, GMPL certificate, list of contractors and labs, Org charts, layouts of production areas, flow charts, schematics of water system, list of major laboratory and production equipment,

31. You have a process where the mean is 3 and the standard deviation is 1. The customer's specification limits are 0 and 6. Which of the following is true?

- A. C_{pk} is larger than C_p
- B. C_p is larger than C_{pk}
- C. They are the same

31. You have a process where the mean is 3 and the standard deviation is 1. The customer's specification limits are 0 and 6. Which of the following is true?

Answer: C. They are the same. Cp and CpK in this case are both 1

$$C_p = (USL - LSL) / 6 \text{ sigma}$$

$$C_{pk} = \text{smaller}\{USL - \text{mean}, \text{mean} - LSL\} / 3 \text{ sigma}$$

32. At least how many repeat media fill process runs should be made during an initial qualification of an aseptic processing line?

A. 10

B. 3

C. 5

D. 17

32. At least how many repeat media fill process runs should be made during an initial qualification of an aseptic processing line?

Answer: B 3

See FDA Guidance for Industry:
Sterile Drug Products Produced
by Aseptic Processing

Handouts

- Body of Knowledge
- This slide presentation
- Summary of FDA vs EU vs Japan vs
(reporting, record retention, Inspection Frequency, etc)
- Definitions (and references where there is information on those subjects)
- Practice test with answers
- Other useful tidbits
- Also sign email sheet and I can send a table of contents and index for many of the references

| Binder | Tab | Description | Where to find (if not specified, google the title) |
|--------|-----|---|--|
| 1 | 1 | 21cfr 7 Enforcement | http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/cfrsearch.cfm |
| 1 | 2 | 9CFR subchapter E 101-117 | http://ecfr.gpoaccess.gov/cgi/t/text/text-idx?c=ecfr&tpl=/ecfrbrowse/Title09/9cfr2_main_02.tpl |
| 1 | 3 | 21 CFR 11 Electronic Records Electronic Signature | http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/cfrsearch.cfm |
| 1 | 4 | 21CFR58 Good Laboratory Practice for Non Clinical Laboratory Studies | http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/cfrsearch.cfm |
| 1 | 5 | 21CFR205 Guidelines for State Licensing of wholesale prescription drugs | http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/cfrsearch.cfm |
| 1 | 6 | 21CFR210 CURRENT GOOD MANUFACTURING PRACTICE IN MANUFACTURING, PROCESSING, PACKING, OR HOLDING OF DRUGS; GENERAL | http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/cfrsearch.cfm |
| 1 | 7 | 21CFR211 CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS | http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/cfrsearch.cfm |
| 1 | 8 | 21CFR600 Biological Products - General | http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/cfrsearch.cfm |
| 1 | 9 | 21CFR601 BiologicsLicensing | http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/cfrsearch.cfm |
| 1 | 10 | 21CFR610 General Biological Products Standards | http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/cfrsearch.cfm |
| 1 | 11 | 21CFR1308 Schedules of Controlled Substances | http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcr/cfrsearch.cfm |
| 1 | 12 | Example of Form 483 | |
| 2 | 1 | General Principles of Software Validation: Final Guidance for Industry and FDA Staff 1/11/2002 | http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064971.htm |
| 2 | 2 | Guidance for Industry Sterile Drug Products Produced by Aseptic Processing | http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064971.htm |
| 2 | 3 | Guidance for Industry Quality Systems Approach to Pharmaceutical CGMP Regulations | http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064971.htm |
| 2 | 4 | Guidance for Industry Q1A(R2) Stability Testing of New Drug Substances | http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm065005.htm |
| 2 | 5 | Guidance for Industry Q1E Evaluation of Stability Data | http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm065005.htm |
| 2 | 6 | Guidance for Industry Q3B Impurities in New Drug Products | http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm065005.htm |
| 2 | 7 | Product Recalls, Including removals and corrections Industry Guidance | |
| 2 | 8 | Guidance for Industry Powder Blends and Finished Dosage Units - Stratified In-Process Dosage Unit Sampling and Assessment | http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064971.htm |
| 2 | 9 | Guidance for Industry for the submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products | google |
| 2 | 10 | Guidance for Industry Changes to an Approved NDA or ANDA | google |
| 2 | 11 | Guidance for Industry and FDA Current Good Manufacturing Practice for Combination Products | http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064971.htm |
| 2 | 12 | Guidance for Industry 1999 Container Closure Systems for Packaging Human Drugs and Biologics Chemistry, Manufacturing and Controls Documentation | google |
| 2 | 13 | Guidance for Industry Container and Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products | google |
| 2 | 14 | Inspection of Biological Drug Products (CBER) 7345.848 Compliance Program Guidance Manual | google |
| 3 | 1 | Administration | Book 3 is the FDA Inspection Manual which has it's own index, so I only had a few items in my index for it. http://www.fda.gov/ICECI/Inspections/IOM/default.htm |

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| Abbreviated inspection, sterile process | 4 | 16 | 4 |
| Abbreviated New Drug Application (ANDA) | 2 | 10/ NDA change | 1 |
| Abbreviations, computer | 5 | 10/ PICS computer and software | 51-52 |
| Abbreviations, pharmaceutical | 2 | 12/ package, human drug and biologic | 31 |
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| acceptance criteria, new drug substance/product polymorphism | 5 | 14/ ICHQ6A Test Accept. Criteria, new dru | 25-26 |
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| act (non clinical lab) | 1 | 4/ 21CFR58 | 1 |

Definitions

Component: Any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product. (21CFR210)

Control Article: Any food additive, color additive, drug, biological product, electronic product, medical device for human use, or any article other than a test article, feed, or water that is administered to the test system in the course of a nonclinical laboratory study for the purpose of establishing a basis for comparison with the test article. (21CFR58)

Critical Process Parameters (CPP): A Process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality. (ICH Q8 (R1)).

Critical Quality Attribute (CQA): A physical, chemical biological or microbiological property or characteristic that should be within an appropriate limit, range or distribution to ensure the desired product quality (ICH Q8 (R1)).

Degradation Product: An impurity resulting from a chemical change in the drug substance brought about during manufacture and/or storage of the new drug product by the effect of, for example, light, temperature, PH, water, or by reaction with an excipient and/or the immediate container closure system (Guidance for Industry Q3B (R2))

Depyrogenation: Process used to destroy or remove pyrogens (e.g. endotoxins) (Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing).

Design Space: The multidimensional combination and interaction of input variables (e.g. material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval (ICH Q8 (R1)).

Detection Limit: Lowest amount of analyte in a sample which can be detected but not necessarily quantitated as an exact value. .

Discontinued Drug Product : Products listed in Drugs@FDA as "discontinued" are approved products that have never been marketed, have been discontinued from marketing, are for military use, are for export only, or have had their approvals withdrawn for reasons other than safety or efficacy after being discontinued from marketing. (Drugs@FDA Glossary of Terms)

Dosage Form : A dosage form is the physical form in which a drug is produced and dispensed, such as a tablet, a capsule, or an injectable. (Drugs@FDA Glossary of Terms)

Summary

- Have references that cover the items in the body of knowledge.
- Have a good subject index so you can look up the material that you don't know.
- Read and Study the references you've put together. If you have to look up everything, then you won't finish the test.
- Create summary sheets for easy to look up things (record retention, etc).
- If you can form study groups to help divide up the effort of getting references and sharing information, that will be a big help.
- Don't take test answer sheets into test.

Conclusion

- Contact Information
gail.keefe@covidien.com
- Sign sheet with email address if you want to form study groups
- Indicate whether you want any of the materials from this workshop sent to you electronically.