Regulations and Resources for the Contamination Control Professional

Presented by:
Dawn McIver,
MicroWorks, Inc.
Agenda

- Purpose of this presentation
- Code of Federal Regulation (CFR)
- cGMPs
- USP
- FDA Guidance Documents
- ISO Standards
Agenda

- European regulations
- PDA Technical Reports
- ICH Guidelines
- ANSI/AAMI
Purpose

- To give an overview of the resources and publications that contamination control professionals should be familiar with.
- To provide an update on changes, revisions on important references and how they may impact operation, Quality and validation activities.
## Sources of Information

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Organization</th>
<th>Website</th>
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<tbody>
<tr>
<td>USP</td>
<td>U.S. Pharmacopeia</td>
<td>uspnf.com</td>
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<tr>
<td>FDA</td>
<td>Food and Drug</td>
<td>fda.gov</td>
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<tr>
<td>PDA</td>
<td>Parenteral Drug Association</td>
<td>pda.org</td>
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<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
<td>ema.europa.eu</td>
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<tr>
<td>ISO</td>
<td>International Organization of Standards</td>
<td>iso.org</td>
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<tr>
<td>ICH</td>
<td>International Council for Harmonization</td>
<td>ich.org</td>
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<tr>
<td>PICs</td>
<td>Pharmaceutical Inspection Co-operation Scheme</td>
<td>Picscheme.org</td>
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<td>WHO</td>
<td>World Health Organization</td>
<td>who.int</td>
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<td>CFR</td>
<td>US FDA</td>
<td>eCFR..gov</td>
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<tr>
<td>EU</td>
<td>European Commission</td>
<td>Ec.Europa.eu</td>
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The CFR contains all the laws governing foods, drugs and cosmetics.

When the FDA inspects a facility they are inspecting based on the CFR.
Important Sections of CFR

- Title 21 pertains to Food and Drugs.
- CFR 21 Parts 210 -226 contain the cGMPs.
- CFR 21 Part 216 contains requirements for pharmaceutical compounding
- CFR 21 Part 810 contains requirements for Medical Devices
- Part 11 contains requirements for electronic records and electronic signatures
Established in 1930

A separate law enforcement agency that regulates over $1 trillion worth of products annually

Commissioner reports directly to the Secretary of the Department of Health and Human Services

When the FDA conducts an investigation in a manufacturing facility, it reports its results on Form 483. This is how a citation has come to be known as a 483.
The Code of Federal Regulations which contains the cGMPs is a book of law.

Non-compliance can result in:
- Product recalls
- Fines of the company or individuals
- Jail time in extreme cases
 Failure to comply with GMPs means the drug is adulterated.
This includes the testing of the drug product.
U.S. Pharmacopeia (USP)

- In 1820, 11 physicians met in D.C. to establish 1st compendium of standard drugs in the U.S
- USP now being published every year
- Amendments are published several times per year
Regulatory Status of USP

- USP is not published by FDA or the government
- Procedures in USP are not laws
- If a drug is labeled USP it is expected to meet current USP specifications
- USP chapters <1000 are mandatory for USP products
- Chapters 1000 to 1999 are interpretive
Updates to USP

• USP-NF is continuously updated.
• Revisions are published annually as Standards Revision and twice annually as Supplements.
• Revisions supersede previous versions so it is important to frequently review the chapters you are utilizing and referencing.
Arrangement of USP

• General Notices-gives basic information regarding expectations when performing USP testing
• Includes rounding rules for assays, terms and definitions, information of the use of reference standards
Arrangement of USP

• USP Monographs-These chapters are arranged alphabetically by the article’s name.

• Monographs contain definition, specification and other requirements related to packaging, storage, and labeling of that product.
Arrangement of USP

• General Chapters-These chapters are assigned a number in angle brackets e.g. <71>

• These chapters have:
  - Descriptions of tests and procedures
  - Specifications of conditions and practices
  - General information for interpretation of compendial requirements
  - General guidance to manufacturers of official substances or official products
Related Chapters

- USP <71>
- USP <85>
- USP <1116>
- USP <1117>
- USP <1223>
- USP <1227>
- USP <51>
- USP <61>
- USP <62>
- USP <1111>
- USP <1072>
- USP <63>
- USP <151>
Related Chapters

- USP <55>
- USP <1229> Series
- USP <1035>
- USP <1209>
- USP <1211>
- USP <1222>
- USP <1112>
- USP <1113>
- USP <1207>
- USP <1208>
- USP <797>
Sterility Testing <71>

- Sterility Testing
- Gives sample preparation, media preparation and QC instructions
- Specifies testing facilities, incubation time and temperature
- Specifies the number of samples
- Specifies procedure and organisms to be used for method validation
- Specific about result interpretation and retesting
Endotoxin <85>

♦ LAL Testing
♦ Gives procedure for performing bacterial endotoxin test (BET) by the LAL Gel Clot Procedure
♦ Describes standards to use
♦ Describes inhibition/enhancement testing (I/E)
♦ Describes test interpretation
Evaluation of cleanrooms for Aseptic manufacturing
Informational Chapter
Recently revised to be specific for aseptic facilities
Companion document in progress that covers non-aseptic facilities
Environmental Monitoring

- Critical factors in design and implementation of EM program
- Development of sampling plan
- Establishment of alert and action levels
- Methodologies and instrumentation used for sampling
- Media and diluents
- Identification of microbial isolate
Alternative Methods <1223>

• Validation of Alternative Microbiological Methods
• Informational chapter
• Describes how to validate alternate technologies
• Validation needs to cover only the part of the test that is being replaced
Validation of Microbial Recovery <1227>

- Informational Chapter
- Specifies what microbial methods need to be validated
- Describes neutralization methods
- Describes chemical inhibition
- Describes how to perform recovery comparisons
Validation of Microbial Recovery from Pharmaceutical Articles

- States that agar tests need three replicates in order to be validated
- Results interpretation (70% recovery)
- Use of alternative medium
- Influential factors in testing
Micro Best Laboratory Practices <1117>

♦ Good laboratory practices depend on using aseptic technique, having control of media used, control of test strains used, control of equipment, diligent recording of data and training of staff.
Antimicrobial Effectiveness <51>

- Details what products require AET testing
- Gives categories of products based on the route of administration
- Gives detailed instructions for organism preparation
- Gives acceptance criteria based on category of drug
Microbial Limits <61>

- Quantitative portion
- Defines TAMC and TYMC - Total Aerobic Microbial Count and Total Yeast and Mold Count
- Gives incubation requirements, media formulations and growth promotion
- Details how suitability is performed
Microbial Limits <62>

- Qualitative portion of Microbial Limits
- Details specified organisms for testing non-sterile products
- Details media, growth promotion and requirements for suitability testing
Microbial Limits Acceptance Criteria <1111>

- Table that gives some guidance on acceptance criteria based on route of administration
- Gives interpretation of acceptance criteria
- Gives guidance on how to evaluate significance of microorganisms recovered
Disinfectant Testing <1072>:

- Details regarding DE Testing on actual surfaces in the facility
- Details organisms to be challenged
- Specifies 3 log reduction for vegetative; 2 log reduction for spore-formers
Each branch of FDA publishes Guidance Documents

List of those published by Center for Drug Evaluation and Research (CDER)

Agency’s current thinking on a particular subject

Available at FDA website, fda.gov
FDA Guidance Documents

- Part 11, Electronic Records, Electronic Signatures-Scope and Application
- Sterile Drug Products Produced by Aseptic Processing (referred to Aseptic guideline)
- Guideline to Inspections of Micro Pharmaceutical QC Labs
FDA Guidance Documents

- Format and Content of the Microbiology Section of an Application
- Good Laboratory Practice Regulations-Questions and Answers
- Investigating Out of Specification (OOS) Test Results for Pharmaceutical Production
Legal Status of Guidelines

“Although guidelines are not legal requirements, a person who follows an agency guideline may be assured that the procedures or standards will be acceptable to the FDA”
FDA Bad Bug Book

• Foodborne Pathogenic Microorganisms and Natural Toxins Handbook
• Can be downloaded from fda.gov
• Full of valuable information
ISO 14644 Series

• Cleanrooms and associated controlled environments
• Part 1: Classification of air cleanliness by particle concentration-New version 12/15
• Part 2: Monitoring to provide evidence of cleanroom performance related to air cleanliness by particle concentration-New version 12/15
Changes in ISO 14644-1

• Formula used to determine number of sampling sites has been replaced with a table.
• The number of sites generally is more than the formula would have indicated.
• The requirement for calculating the 95% confidence interval has been removed.
Changes in ISO 14644-2

- Changes were made to simplify the tables that specify frequency of testing
- Refined how the intervals may be extended when automated systems are used to demonstrate control
- New guidance added on configuring a monitoring system
ISO 14644 Series

- Part 3: Test Methods
- Part 4: Design, Construction and Start Up
- Part 5: Operations
- Part 6: Vocabulary
- Part 7: Separative devices (clean air hoods, gloveboxes, isolators and minienvironments)
ISO 14644 Series

• Part 8: Classification of airborne molecular contamination
• Part 9: Classification of surface particle cleanliness
• Part 10: Classification of surface cleanliness by chemical concentration
• Part 12: Classification of Air Cleanliness by Nanoscale Particle Concentration
ISO 14698

• Part 1: Biocontamination control-General principles and methods
• Part 2: Evaluation and interpretation of Biocontamination data
ISO 8573 Compressed air

• Part 1: Contaminants and purity classes
• Part 2: Test methods for oil aerosol content
• Part 3: Test methods for measurement of humidity
• Part 4: Test methods for solid particle content
ISO 8573 Compressed air

- Part 5: Test methods for oil vapour and organic solvent content
- Part 6: Test methods for gaseous content contaminant content
- Part 7: Test method for viable microbiological contaminant content
ISO 8573 Compressed air

- Part 8: Test methods for solid particle content by mass concentration
- Part 9: Test methods for liquid water content
Other Pharmacopeia

• If products will be sold outside the US they need to comply with the requirements in that country

• Some chapters such as Sterility, Microbial Limits and Endotoxin have been harmonized between US, EU and Japan

• Don’t assume the requirements are the same without checking.
European Regulations

- Countries include: Austria, Belgium, Bulgaria, Croatia, Republic of Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and the UK.
European Regulations

- EudraLex: The Rules Governing Medical Products in the EU
- Volume 4: GMP Guidelines
- EU Annex 1: Manufacture of Sterile Medicinal Products
EU Annex 1

- Cleanroom classifications based on the use of the area: Grade A, B, C and D
- Table details the maximum number of 0.5 micron particles per cubic meter of air
- For Grade A areas a minimum of 1 cubic meter of air should be taken per sampling location. ISO classification is 4.8
PDA Technical Report

• PDA had published a number of technical reports to help members interpret regulatory requirements and provide details that may be missing from official documents.

• PDA Guidelines are not regulatory requirements but they provide valuable information to industry users.
Useful PDA Technical Reports

• TR1: Validation of Moist Heat Sterilization, updated 2007
• TR9: Points to Consider for Cleaning Validation, Revised 2012
• TR13: Fundamentals of an Environmental Monitoring Program, Revised 2014
Useful PDA Technical Reports

• TR33: Evaluation, Validation and Implementation of Alternative and Rapid Microbiological Methods, Revised 2013
• TR34: Design and Validation of Isolator Systems, 2001
• TR 51: Biological Indicators for Gas and Vapor-Phase Decontamination Processes: Specif., Manufacture, Control and Use, 2010
Useful PDA Technical Reports

• TR67: Exclusion of Objectionable Microorganisms from Nonsteriles, 2014
• TR69: Bioburden and Biofilm Management in Pharm. Manufacturing Operations, 2015
• TR 70: Fundamentals of Cleaning and Disinfection Programs for Aseptic Manufacturing Facilities, 2015
ICH Guidelines

• International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH)
ICH Guidelines

- Q1A-Q1F: Stability
- Q2: Analytical Validation
- Q7: Good Manufacturing Practices
- Q8: Pharmaceutical Development
- Q9: Quality Risk Management
- Q10: Pharmaceutical Quality System
AAMI/ANSI

- ANSI/ASQ Z1.4-2003: Sampling Procedure and Tables for Inspection Attributes
Conclusion

- Resources and information are abundant.
- Be aware of where the requirements come from for applicable testing.
- Use updates and educational resources to keep informed of changes.
- Avoid references that you are not using.
- Remember the c of cGMPs