USP <1115> Bioburden Control of Non-sterile Drug Substances and Products: Intent, Implementation and Impact

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Disclosures

• The opinions expressed in this presentation are solely mine and not those of my former employer Merck & Co, the USP Microbiology Committee of Experts or my current consulting clients.
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Congratulations.
Presentation Outline

• The intention of the USP Microbiology Committee of Experts
• Implementation of the USP Chapter
• Expected impact of the new USP chapter <1115>
• Extent of microbial contamination of non-sterile drug products
• Content of the USP Chapter <1115>
• Risk hierarchy by dosage form
• Factors increasing microbial contamination risk
• Drug substances
• Pharmaceutical excipients
• Drug Products
• Role of Manufacturing
What is the USP?

• The U.S. Pharmacopeial Convention Inc. is an independent standards organization, founded in 1820, empowered by the U.S. Federal Food, Drug, and Cosmetic (FD&C) Act as the official drug standard-setting organization in the U.S. for drug products.

• The Pharmacopeial Convention publishes and maintains the United States Pharmacopoeia (USP), National Formulary (NF), and USP Reference Standards and sets the quality standards for both drug products and pharmaceutical ingredients.
U.S. Pharmacopeia

• Hard Copy

• Electronic Copy
• May be download from the USP website:
  www.usp.org/usp-nf/offical-text

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IVT Microbiology Week
USP Intention

• The new USP Informational Chapter <1115> Bioburden Control of Non-sterile Drug Substances and Products was published in the 2nd Supplement to USP37-NF32 July 2014. What was the intent of the USP in publishing this chapter?

• In the absence of regulatory guidance, the USP has provided a pragmatic scientific approach to the management of the microbial bioburden in non-sterile drug products in keeping with patient risk and contamination control objectives based on risk management principles.
USP Intention

• The chapter contains information on microbial control considerations in product development, routine manufacturing, equipment design and use, microbial assessment of the non-sterile manufacturing environment, active measures for microbial control, and the overall management of a microbiological control program.

• Note: It is an informational chapter and not an enforceable compliance document.
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Industry Implementation

• How should drug substance and drug product manufacturers react to the publication of this chapter?

• I would hope that they should adopt a more risk-based approach to bioburden control in non-sterile drug development and manufacturing based on an understanding of what determines the presence of microorganisms in their manufacturing facilities and their persistence or proliferation in their drug products.
Expert Opinion

• David Hussong, FDA CDER Microbiology Director, stated: “For the microbiologist, this (quality initiatives) emphasizes the importance of process knowledge to replace reliance on testing samples of finished product. Avoiding microbiological adulteration yields a more reliable indicator of quality, which agrees with the assertion that quality cannot be tested into the product.”
Industry Implementation

• Manufacturers should appreciate that whether microorganisms found in a non-sterile product will be objectionable in that product depends their number and species, the product attributes, dosing regimen, route of administration, and targeted patient population.

• Any environmental monitoring program would be risk-based in terms of sample selection and frequency and would be used to confirm microbial control and would not be linked to product release.
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Industry Impact

• What is the expected impact of the USP chapter?
• The expectation is there would be improved and cost-effective bioburden controls for non-sterile drug products to a level consistent with patient safety.
• This may reduce product recalls for microbial contamination.
• Manufacturers will be able to benchmark their bioburden control programs against the recommendations within the chapter and adjust their programs accordingly.
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Microbial Contamination

• The contamination of marketed products with objectionable microorganisms continues to be an infrequent but chronic problem for our industry.

• There are the order of 20 U.S. recalls on non-sterile products annually for microbial contamination.
What are Objectionable Microorganisms?

- They are defined by specific dosage forms.
- They include specified microorganisms, frank pathogens and opportunistic pathogens that are known from the clinical literature to cause infection in the recipient via the route of administration or microorganisms that grow in the product overcoming the preservative system.
- Also, they may include organisms associated with major recalls for microbial contamination.
- If these microorganisms are present in the drug product below the microbial limit, the batch would be rejected.
U.S. Congressional Hearings
U.S. Recalls

• A recent U.S. survey reported 144 recalls composed of non-sterile branded pharmaceutical drug products (5%), over-the-counter drug products (42%), cosmetics (31%), medical devices (14%) and dietary supplements (8% of the total recalls) for microbiologically-related issues for the 7-year period from 2004 through 2011.

• The survey highlighted that the majority of these recalls (72%) were associated with objectionable microorganisms and not for exceeding the microbial enumeration limits (Sutton and Jimenez, 2012).
Microorganisms Implicated

• The most frequently cited microorganisms in the recalls were the *Burkholderia cepacia* complex (34 occurrences), unspecified fungal contamination (19 occurrences), *Bacillus cereus* (9 occurrences), *Pseudomonas aeruginosa* (6 occurrences), *Elizabethkingia meningoseptica* (5 occurrences), *Enterobacter gergovia* (5 occurrences), *Pseudomonas putida* (3 occurrences), *Pseudomonas* spp. (2 occurrences) and *Salmonella* spp. (2 occurrences).
Burkholderia cepacia Complex

• The prominence of the Gram-negative, oxidase-positive bacterium *B. cepacia* in non-sterile product recalls is the result of its prevalence in water, metabolic versatility, and its resistance to many disinfectants and antimicrobial preservative systems.

• *B. cepacia* is a common opportunistic pathogen and infects cystic fibrosis sufferers.
Unidentified Fungi

- The second most prevalent recall category was unidentified fungi. This reinforces that pharmaceutical microbiologists do a poor job identifying mold.
- For further information see Cundell, A. M. 2013 *Mold Contamination in Pharmaceutical Drug products and Medical Devices* European Pharmaceutical Review 18 (6): 67-75
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Contents of the USP Chapter

• Introduction
• Risk Hierarchy
• USP <61>, <62> and <1111>
• US Regulatory Guidance Documents
• Microbial Control Consideration During Product Development
• Microbial Control Consideration During Manufacturing
• Microbial Control of Drug Substance Manufacturing
  – Equipment Design and use
  – Personnel
  – The Manufacturing Environment
Content of the USP Chapter

• Microbial Assessment of Non-sterile Product Manufacturing Environment
  – Microbial Sampling
  – Microbial Identification
  – Active Measures for Microbial Control

• Overall Management of a Microbiological Control Program

• References
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  • Risk hierarchy by non-sterile dosage form
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  • Drug substances
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  • Manufacturing
Risk Hierarchy

Hierarchy of risk due to microbial contamination by route of administration (High to low):

- Metered-dose and dry powder inhalants
- Nasal sprays
- Otics
- Vaginal suppositories
- Topicals
- Rectal suppositories
- Oral liquids (aqueous)
- Liquid-filled capsules
- Compressed tablets and powder-filled capsule
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• Other factors increasing microbial contamination risk
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• Manufacturing
Increased Microbial Risk

• The development of novel drug delivery systems e.g., dry powder inhalants, nasal sprays, transdermal patches, and drug-coated transplanted medical devices that may increase patient risk to microbial contamination due to their invasiveness within the human body.

• The sourcing of drug substances from manufacturing facilities in third-world countries with increased risk of potential product contamination due to poor GMPs.

• Globalization with drugs manufactured outside the US and transported around the world.
Increased Microbial Risk

• The growth of off-label dosage regimes and patient populations as physicians seek wider clinical applications and change administration practices.

• The increased aggressiveness and invasiveness of medical treatments.

• Increases in patients who due to their age or medical condition are seriously immunologically compromised and are aggressively treated.
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Drug Substances

• The bioburden of DS manufactured by chemical synthesis will largely depend on the final synthetic, isolation and purification steps, the drying process, micronization for particle size reduction, and to a lesser extent the drug substance packaging.

• In general, the chemical transformations and isolation of intermediates typically involve reactions using reagents, solvents, and elevated temperatures that are incompatible with the survival of microorganisms.
Chemical Synthesis
Drug Substances

• The bioburden of the starting materials, reagents, and intermediates will have little or no impact on the bioburden of the drug substances and may be discounted.

• The bioburden of a plant- or animal-derived drug substance will depend on the degree of processes of the material.
Drug Substances

• The impact of the final purification and isolation steps on the DS bioburden depends on the solvent used in the mother liquor, temperature of the isolation process, the inclusion of a bioburden-controlling filtration step, the material recovery method, and drying process.

• Typically 90% of the isolations employ organic solvent or a mixture of organic solvents and water and not water, which reduces the likelihood of microbial contamination.
Drug Substances

• The most common organic solvents used in industrial organic syntheses include toluene, tetrahydrofuran, dichloromethane, ethyl acetate, 2-propanol, methanol, denatured alcohol, acetic acid, n-heptane, and acetronitrile. All are inimical to the survival of microorganisms.

• If water is the primary solvent, purified water, USP is used for DS used in non-sterile drug products and low-endotoxin purified water in sterile drug products.
Product Development

Points to be considered when assessing the potential microbial risk associated with non-sterile drug products:

• Synthesis, isolation and final purification of the drug substance
• Microbiological attributes of the drug substance
• Formulation and physicochemical attributes of the drug product
• Water activity of the drug product
• Manufacturing process
• Packaging and delivery system
• Storage conditions of the drug substance and product
• Route of administration
• Expected treatment procedure and dosage regimen
• Age and health condition of the intended recipients of the drug
U.S. Regulatory Documents

- FDA Good Manufacturing Practices found in 21 CFR Part 211
- 211.42 Design and Construction
- 211.46 Ventilation, Air Filtration. Air heating and Cooling
- 211.56 Sanitation
- 211.113 Control of Microbiological Contamination
Manufacturing Risk Factors

Microbial risk factors in descending order:

• Ingredient water
• Pharmaceutical ingredients
• Processing equipment
• Manufacturing personnel
• Manufacturing environment
Pharmaceutical Water Systems
## Classification of Pharmaceutical Excipients

- Binders
- Disintegrants
- Fillers (diluents)
- Lubricants
- Glidants (flow enhancers)
- Compression aids
- Colors
- Sweeteners
- Caking agents
- Buffers
- Preservatives
- Suspending/dispersing agents
- Film formers/coatings
- Flavors
- Printing inks
## Common Excipients used in Solid Dosage Forms

<table>
<thead>
<tr>
<th>Excipient Classification</th>
<th>Common Excipients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diluent or Filler</td>
<td>Lactose, Sucrose, Kaolin, Dibasic Calcium Phosphate, Calcium Sulfate, and Calcium Carbonate</td>
</tr>
<tr>
<td>Binders</td>
<td>Water, Alcohol, Starch Paste, Gelatin Solutions, Tragacanth, Sodium Alginate, Carboxymethyl Cellulose, Polyethylene Glycol and Povidone</td>
</tr>
<tr>
<td>Lubricants</td>
<td>Magnesium Stearate, Calcium Stearate, Talc, Stearic Acid, Starch, Mineral Oil, Sodium Chloride, Sodium Benzoate, and Carbowax 4000 or 6000</td>
</tr>
<tr>
<td>Disintegrating Agents</td>
<td>Corn Starch, Methylcellulose, Sodium Carboxymethyl Cellulose, Alginic Acid, Microcrystalline Cellulose and Gums</td>
</tr>
<tr>
<td>Sweetening Agents</td>
<td>Mannitol, Lactose, Sorbitol, Fructose, Saccharine, and Aspartame</td>
</tr>
</tbody>
</table>
## Risk Analysis of Pharmaceutical Excipients

<table>
<thead>
<tr>
<th>Classification</th>
<th>Examples of Excipients</th>
<th>Microbial Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synthetic Material</td>
<td>Povidone (polyvinyl pyrrolidone) and Crospovidone (A homopolymer of cross-linked N-vinyl-2 pyrrolidone)</td>
<td>Little or none</td>
</tr>
<tr>
<td>Semi-synthetic material</td>
<td>Captisol (Chemically-modified cyclodextrin) and Hydroxypropyl Methylcellulose</td>
<td>Low to moderate</td>
</tr>
<tr>
<td>Plant-derived Material</td>
<td>Corn Starch, Microcrystalline Cellulose, and Sucrose</td>
<td>Moderate</td>
</tr>
<tr>
<td>Animal-derived Material</td>
<td>Lactose (Extractive), Magnesium Stearate (Processed chemically from tallow), and Gelatin (Purified from bone or hide)</td>
<td>Moderate to high</td>
</tr>
<tr>
<td>Mineral-derived Material</td>
<td>Talc (Extractive) and Dibasic Calcium Phosphate (Processed chemically from a mineral calcium carbonate and phosphoric acid)</td>
<td>Low to moderate</td>
</tr>
</tbody>
</table>
Talc Mining
Lactose Production

- Whey protein concentrates are powder made by drying the retentate from the Ultra Filtration of whey. The concentration of whey proteins is primarily achieved by UF and Diafiltration.

- The permeate of UF membrane is high in lactose content, so that is used for manufacturing lactose powder. Permeate recovered is concentrated to minimum 62% TS level in an evaporator and then cooled under controlled conditions for Lactose crystallization. Crystals are washed, decanted and spray dried to produce pharma grade lactose.
Lactose Manufacturing

- Lactose spray dryer
Risk Assessment

- In Failure Mode and Effects Analysis (FMEA) terms risk was defined in terms of occurrence (O), severity (S) and detection (D). The risk is expressed as $O \times S \times D$. Using this tool, risk is minimized if occurrences decrease, severity of the effect of failure is decreased, and the efficiency of detection of a failure increases.

- Note: The less readily that microbial contamination can be detected the higher the value of D and the overall risk.

- For a discussion of risk analysis see ICH Q9 Quality Risk Management
Simple Risk Analysis

An approach is to assign a score from 1 to 3 to the following:

- Severity (S) as a consequence of failure
- Occurrence (O) as the likelihood of failure occurring based on past experience
- Detection (D) as the likelihood that failure detection will take place with the proposed monitoring system
- The risk is determined by the product of \( S \times O \times D \)
Risk Analysis – Occurrences (O), Susceptibility (S) and Detectability (D)

<table>
<thead>
<tr>
<th>Excipient Manufacturing Process</th>
<th>O</th>
<th>S</th>
<th>D</th>
<th>O x S x D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synthetic Material</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Semi-synthetic material</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Plant-derived Material</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>Animal-derived Material</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>18</td>
</tr>
<tr>
<td>Mineral-derived Material</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>8</td>
</tr>
</tbody>
</table>
ICH Q6A

• For drug product release testing, ICH Q6A Test Procedures and Acceptance Criteria for New Drug Substances and Drug Products provides decision trees that guide manufacturers on necessary test strategies based on the nature of the product.

• The establishment of microbiological attributes are described in Decision Tree 6 (Drug Substances) and Decision Tree 8 (Drug Products).

• Low water activity is a highlighted attribute for reduced testing strategies.
Manufacturing Environment

Common design elements to control microbial contamination:

• Non-porous walls, ceilings and floors that are readily cleanable
• Floor drains that can be closed during processing or fitted with an air break if opened during area and equipment cleaning
• Access should be limited to essential personnel
• Material, equipment and personnel flows should avoid contamination
• Ventilation and air filtration should be adequate to maintain the specified cleanliness, space pressurization, temperature and humidity
Manufacturing Equipment

For bioburden control equipment should have the following attributes:

• Sanitary design
• Readily cleaned preferably using a CIP system
• Self-draining to eliminate stagnate water
• Preventative maintenance program to periodically replace valves, seals, filters and hosing
• Inclusion of microbial monitoring in cleaning validation protocols
Dosage Forms

- Over 80% of the current drug products by the number of prescription are marketed as oral solid dosage forms, i.e. powder- and liquid- filled capsules and compressed tablets, which have a very low risk of microbial contamination because of their manufacturing processes, low water activity and route of administration.

- Many other non-sterile drug products, e.g., oral liquids, topicals, nasal sprays, etc, may be susceptible to microbial growth and have more critical routes of administration than an oral solid.
Risk Assessment

What other tools are available for this risk assessment?

- In the 1960's, the Pillsbury Company, the U.S. Army, and National Aeronautics and Space Administration (NASA) introduced a system for assuring pathogen-free foods for the space program.

- This system, called Hazard Analysis and Critical Control Points (HACCP), is a focus on critical food safety areas as part of total quality programs and may be a tool applicable to the pharmaceutical industry.
HACCP

• HACCP involves a critical examination of the entire food manufacturing process to determine every step where there is a possibility of physical, chemical, or microbiological contamination of the food, which would render it unsafe or unacceptable for human consumption. These identified points are the critical control points (CCP).
HACCP

There are seven principles to HACCP:

1. Analyze hazards,
2. determine CCPs,
3. establish critical limits,
4. establish monitoring procedures,
5. establish deviation procedures,
6. establish verification procedures, and
7. establish record keeping procedures
Tablet Manufacturing

- In general, the most critical processing steps with respect to potential microbial contamination are the procurement of pharmaceutical ingredients, wet granulation and milling and tablet coating (Bolded red in list of manufacturing steps). For example, the holding time of aqueous film coating solutions may be a critical control point.

- In contrast, fluid bed drying and compression are potentially bioburden-reduction steps (Bolded green)
Tablet Manufacturing

For example, the processing steps for the manufacture of a film-coated compressed tablet are:

- Procurement of pharmaceutical ingredients
- Warehousing pharmaceutical ingredients
- Batching of the pharmaceutical ingredients
- Blending
- Wet granulation and milling
- Drying
- Tablet compression
- Tablet coating
- Packaging
- Distribution
Tablet Manufacturing

- Unit processes involved in making tablets include particle size reduction and sizing (milling), blending, granulation, drying, compaction (compression), (frequently) coating and packaging.
Tablet Manufacturing
## Risk Analysis for Tablet Manufacturing

<table>
<thead>
<tr>
<th>Manufacturing Step</th>
<th>Contamination Potential</th>
<th>Preventative Measures/Critical Control Points</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wet granulation and milling</td>
<td>Moderate</td>
<td>Equipment design. Cleaning validation. Monitor purified water used in granulation solutions for microbial counts (CCP). Holding Time (CCP).</td>
<td>Emphasis on water system validation and equipment cleaning to prevent microbial contamination. Water activity measurement may be used to evaluate the ability of the granulation to support microbial growth</td>
</tr>
</tbody>
</table>
## Risk Analysis for Tablet Manufacturing

<table>
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</table>
| Tablet Coating     | Moderate to High          | Equipment cleaning and solution holding time (CCP)  
Incoming microbial testing of ingredients (CCP)  
Monitor purified water used in coating solutions for microbial counts (CCP) | Water-based coating solution will support microbial growth. Holding times need to be justified. |
Risk Analysis

- After Anastasia Lois, 2013
Conclusions

The management of a successful microbiological control program includes the following:

• Identification of suitable suppliers of pharmaceutical ingredients and excipients that have good microbiological quality

• Conducting a microbial risk assessment of the drug formulation, manufacturing process and packaging system and mitigating those risks

• The establishment of an appropriate monitoring and control system.
Contact Information

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