Microbial Contamination Risk Assessment

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Disclaimer

• The opinions expressed in this presentation are my entirely my own and not that of the USP Microbiology Expert Committee or my consulting clients.
Presentation Overview

Quality Risk Management Tools

• Survey of Quality Risk Management Tools – Fault Tree analysis (FTA), Failure Mode Effects Analysis (FMEA), Hazard Analysis Critical Control Points (HACCP), Total Quality Control (TQC), ISO 9001, ICH Q8, Q9 and Q10
Presentation Overview

Sterile Products

• Sterile Injectable Drug Products - Aseptically-filled versus Terminally-sterilized Products

• Critical Quality Attributes of Sterile Products - Sterility, Endotoxin Levels and Absence of Mycoplasma and Adventitious Viruses

• Critical Process Parameters - Bioburden Monitoring and Control and Sterilization Processing

• Risk Mitigation
Presentation Overview

Non-sterile Drug Products

• Critical Quality Attributes of Non-sterile Products - Microbial Count, Absence of Specified Microorganisms, and Absence of Objectionable Microorganisms

• Risk Hierarchy by Dosage Form

• Role of Formulation and Product Attributes

• Role of Unit Processing Steps

• Risk Mitigation
Presentation Overview

Class Exercise

• Application of Risk Assessment Tools to the risk assessment for a film-coated compressed tablet
Risk Awareness

THE ANNUAL DEATH RATE AMONG PEOPLE WHO KNOW THAT STATISTIC IS ONE IN SIX.

CRACK

BOOM

WHOA! WE SHOULD GET INSIDE!

IT’S OKAY! LIGHTNING ONLY KILLS ABOUT 45 AMERICANS A YEAR, SO THE CHANCES OF DYING ARE ONLY ONE IN 7,000,000. LET’S GO ON!
Definitions of Risk

• “The possibility that something bad, unpleasant or dangerous may happen.” Dictionary of Contemporary English.

• Risk = Frequency (event/time) x Severity or Magnitude (consequences/event). Islam et al, 2012

• Risk is the combination of the probability of occurrence of harm and the severity of the harm. ICH Q9 2005
Top Ten Causes of Death Annually in the U.S. (CDC 2009)

• Heart Disease – 598,000; 180 per 100,000
• Cancer – 568,000; 174 per 100,000
• Chronic Respiratory Disease – 137,000; 42 per 100,000
• Stroke – 128,000; 39 per 100,000
• Accidents – 117,000; 37 per 100,000
• Alzheimer’s Disease – 79,000; 23 per 100,000
• Kidney Disease – 48,000; 15 per 100,000
• Diabetes – 68,000; 21 per 100,000
• Flu & Pneumonia 54,000; 16 per 100,000
• Suicide – 36,000; 12 per 100,000
Other Lower Risks of Death Annually

- Skydiving – 25
- Dog Bites – 34
- Hit By Lightning – 50
- Falling Out Of Bed – 450
- Drowning – 4,000
- Firearms – 32,000
- Automobile Accidents – 43,000
- Infectious Disease – 75,000
Prescription Drugs - Job Ratings

• In a national survey asking who was doing a good job ensuring the safety and efficacy of prescription drugs the public responded as follows:
  • Pharmacists – 73%
  • Physicians – 58%
  • Hospitals – 54%
  • Federal regulatory agencies – 52%
  • Patients – 46%
  • Drug manufacturers – 42%
  • Patients health plan – 24%

Slovic et al, 2007 Drug Information Journal 41: 81-100
# Risk-Benefit Quadrant

## Risk-Benefit Quadrant (List in Descending Order of Risk)

<table>
<thead>
<tr>
<th>Low Risk-High Benefit</th>
<th>High Risk-High Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Household Cleaner</td>
<td>Pesticides</td>
</tr>
<tr>
<td>Drugs for Erectile Dysfunction</td>
<td>Nuclear Power Plants</td>
</tr>
<tr>
<td>Biotech Drugs</td>
<td>Cancer Chemotherapy</td>
</tr>
<tr>
<td>Air Travel</td>
<td>Heart Surgery</td>
</tr>
<tr>
<td>Smallpox Vaccination</td>
<td>Automobiles</td>
</tr>
<tr>
<td>Birth Control Drugs</td>
<td>Drugs for AIDS</td>
</tr>
<tr>
<td>Vaccines</td>
<td>Hormone Replacement Therapy</td>
</tr>
<tr>
<td>Prescription Drugs</td>
<td>Antidepressants</td>
</tr>
<tr>
<td>High Blood Pressure Drugs</td>
<td>Anti-anxiety Drugs</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>IUD</td>
</tr>
<tr>
<td>Allergy Drugs</td>
<td></td>
</tr>
<tr>
<td>Mammograms</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Low Risk-Low Benefit</th>
<th>High Risk-Low Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetically Modified Foods</td>
<td>Cigarette Smoking</td>
</tr>
<tr>
<td>Food Additives</td>
<td>High Fat Foods</td>
</tr>
<tr>
<td>Artificial Sweeteners</td>
<td>Alcoholic Beverages</td>
</tr>
<tr>
<td>Coffee</td>
<td>Botox Injections</td>
</tr>
<tr>
<td>Acupuncture</td>
<td>Diet Drugs</td>
</tr>
</tbody>
</table>

- Risk-Benefit Quadrant: List in Descending Order of Risk
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IVT Annual Microbiology Week
# Risk Mapping

<table>
<thead>
<tr>
<th>Consequence</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>MEDIUM</td>
<td>HIGH</td>
<td>HIGH</td>
<td>CRITICAL</td>
<td>CRITICAL</td>
</tr>
<tr>
<td>4</td>
<td>LOW</td>
<td>MEDIUM</td>
<td>HIGH</td>
<td>HIGH</td>
<td>CRITICAL</td>
</tr>
<tr>
<td>3</td>
<td>LOW</td>
<td>LOW</td>
<td>MEDIUM</td>
<td>HIGH</td>
<td>HIGH</td>
</tr>
<tr>
<td>2</td>
<td>VERY LOW</td>
<td>LOW</td>
<td>LOW</td>
<td>MEDIUM</td>
<td>HIGH</td>
</tr>
<tr>
<td>1</td>
<td>VERY LOW</td>
<td>VERY LOW</td>
<td>LOW</td>
<td>LOW</td>
<td>MEDIUM</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
</tr>
</tbody>
</table>
Low Probability, High Severity
Risk Mitigation Decisions

- Mitigate or Reduce Risk
- Avoid the Risk
- Accept Risk
- Share or Transfer Risk
Evaluation of the risk to quality must be based on scientific knowledge and ultimately link to the protection of the patient.

Level of effort, formality and documentation of the quality risk management process must be commensurate with the level of risk.
Quality Risk Management Tools

Our vision: The future Pharmaceutical Quality System

Quality Risk Management

For companies with:
1. Good design and control strategies
2. Good Risk Management strategies
3. Good Quality Systems

Reduced regulatory burden:
• Reduction of submissions on changes/variations
• Inspection of quality systems

The Regulatory Quality System

Quality Risk Management (Q9)

Quality by Design (Pharmaceutical Development) (Q8)

Quality Systems (Q10)

Quality Systems

Existing GMP’s

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In 1978 21 CFR Parts 210 Current Good Manufacturing Practice in Manufacturing, Processing, Packaging or Holding Drugs: General and 211 Current Good Manufacturing Practice for Finished Pharmaceuticals were finalized.

In 1987 FDA Guideline on General Principles of Process Validation was published.

Note: Drug products manufactured with GMP violation are considered adulterated in terms of the Food, Drug and Cosmetic Act and may be subjected to regulatory action.
ICH Q9: *Pharmaceutical Quality Risk Management* (QRM) Benefits and Challenges:

- QRM can provide a framework for the microbial contamination risk assessment recommending tools like FMEA, FTA, HACCP, cause and effect diagrams and other statistical tools.
Quality Risk Management Process

Initiate Quality Risk Management Process

Risk Assessment
- Risk Identification
- Risk Analysis
- Risk Evaluation

Risk Control
- Risk Reduction
- Risk Acceptance

Output / Result of the Quality Risk Management Process

Risk Review
- Review Events

Risk Management tools

unacceptable
ICH Q8 Pharmaceutical Development 2009 states that a Quality by Design (QbD) approach would include the following:

- A systematic evaluation, understanding and refining of the formulation and manufacturing process, including identifying and determining the functional relationships of the material attributes and process parameters that can have an effect on product critical quality attributes
Quality Risk Management Documents

• ICH Technical Requirements for Registration of Pharmaceuticals for Human Use Q10 Pharmaceutical Quality Systems 2008
• EU GMP Guide Annex 15
ICH Q10 Document

- ICH Q10 describes an effective pharmaceutical quality system based on ISO quality concepts that can be implemented throughout the different stages of a product lifecycle, i.e., pharmaceutical development, technology transfer, commercial manufacturing and product discontinuation.
FMEA

Score (from 1 to 5) each of the following categories:
• Severity (S)
• Frequency of occurrence (O)
• Ease of detection (D)

Using these criteria, a final FMEA score is the sum of:
• Severity score x Occurrence score x Detection score
  or S x O x D
HACCP

• Hazard Analysis Critical Control Points (HACCP) was first developed to prevent food borne infection in astronauts by NASA, the food company Pillsbury, and US Army Natick Center.

• This program is widely used in the food industry
HACCP

The seven principles used in HACCP analysis are:
1. Identifying hazards and assessing their severity.
2. Determining the Critical Control Points (CCPs)
3. Establishing control limits
4. Establishing system to monitor and control CCPs
5. Establishing corrective actions when a CPP is not under control.
6. Establishing procedures to verify HACCP system is effectively working
7. Establish in a documentation and reporting system
### Risk Management Maturity (M. Long, 2013)

<table>
<thead>
<tr>
<th>Risk Maturity Level</th>
<th>Risk Processes</th>
<th>Attitude</th>
<th>Behavior</th>
<th>Skill &amp; Knowledge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skepticism</td>
<td>No formal processes</td>
<td>“Accidents will happen”</td>
<td>Fear of blame’ culture</td>
<td>Unconscious incompetence</td>
</tr>
<tr>
<td>Awareness</td>
<td>Isolated use of stand-alone processes</td>
<td>Suspended belief</td>
<td>Reactive, ‘fire fighting’</td>
<td>Conscious incompetence</td>
</tr>
<tr>
<td>Understanding and application</td>
<td>Extended use of combined processes</td>
<td>Passive acceptance</td>
<td>Compliance thinking</td>
<td>Conscious competence</td>
</tr>
<tr>
<td>Embedding and integration</td>
<td>Risk management embedded in the business</td>
<td>Active engagement</td>
<td>Risk-based decision making</td>
<td>Unconscious competence</td>
</tr>
<tr>
<td>Robust risk management</td>
<td>Frequent risk review and improvement</td>
<td>Champion</td>
<td>Innovative and appropriate risk management</td>
<td>Expert</td>
</tr>
</tbody>
</table>
Cause and Effect Diagram
Contaminated Product

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Critical Quality Attributes

What is a Critical Quality Attribute (CQA)

- A quality attribute that must be controlled within predefined limits to ensure that the drug product meets its intended safety, efficacy, stability and performance
- What are the CQA for microbiological attributes?
Critical Microbiological Attributes

• Sterile products – Sterility, absence of mycoplasma and adventitious viruses and bacterial endotoxin level
• Non-sterile products – Microbial enumeration, absence of specified microorganisms and absence of objectionable microorganisms
• Note: Container-Closure Integrity, antimicrobial effectiveness (aqueous multi-use products) and water activity are development parameters only
Critical Microbiological Attributes

Compendial Tests for Sterile Products:
• USP <63> Mycoplasma Tests
• USP <71> Sterility Tests
• USP <85> Bacterial Endotoxins Tests

Note: Unless fully justified, use a terminal sterilization process over an aseptic filling process.
Critical Microbiological Attributes

Non-sterile Drug Products:

• USP <61> Microbiological Examination Tests: Microbial Enumeration

• USP <62> Microbiological Examination Tests: Absence of Specified Microorganisms

• 21 CFR 211.113 Absence of Objectionable Microorganisms
Product Development Testing

• USP <51> Antimicrobial Effectiveness Testing
• USP <1112> Application of Water Activity Determination to Non-sterile Pharmaceutical Products
• USP <1207> Sterile Product Packaging – Integrity Evaluation
## Risk Analysis – Sterile Products

<table>
<thead>
<tr>
<th>Dosage Form</th>
<th>Risk Rating</th>
<th>Unit of Operation</th>
<th>Risk Rating</th>
<th>Overall Risk Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biological Injectable</td>
<td>5</td>
<td>Bioreactor – Sterilization, Inoculum Production, Biofermentation, Recovery, and Downstream Purification Cell Bank Maintenance, and Viral Clearance Sterile Filtration, Aseptic Filling, Lyophilization and Stoppering and Capping</td>
<td>4 3 4 5</td>
<td>5</td>
</tr>
<tr>
<td>Pharmaceutical Injectable</td>
<td>4</td>
<td>Aseptic Filling: Traditional Cleanrooms Aseptic Filling: Form-fill-seal or Isolator System Terminal Sterilization</td>
<td>5 3 1</td>
<td>4</td>
</tr>
<tr>
<td>Sterile inhalation Solution</td>
<td>4</td>
<td>Aseptic Filling: Traditional Clean Rooms Aseptic Filling: Form-fill-seal or Isolator System Terminal Sterilization</td>
<td>5 3 1</td>
<td>4</td>
</tr>
</tbody>
</table>
Other Key Documents

• FDA Guidance for Industry on Sterile Drug Products Produced by Aseptic Processing 2004
• EU Guidelines to Good Manufacturing Practice Medicinal Products for Human and Veterinary Use Annex 1: Manufacture of Sterile Medicinal Products 2008
• PDA Technical Report No. 44 Quality Risk Management for Aseptic Products
## Risk Analysis - Non-sterile Products

<table>
<thead>
<tr>
<th>Dosage Form</th>
<th>Risk Rating</th>
<th>Unit of Operation</th>
<th>Risk Rating</th>
<th>Overall Risk Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metered Dose Inhalant</td>
<td>4</td>
<td>Micronization, Blending, Filling/Assembling</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Topical Liquid, Lotion or Cream</td>
<td>3</td>
<td>Mixing and blending, Filling</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Topical Gel or Ointment</td>
<td>2</td>
<td>Emulsification, Blending, Heating and Cooling, Dispensing</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Oral Liquid or Suspension</td>
<td>3</td>
<td>Mixing and blending, Filling</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Transdermal Patch</td>
<td>2</td>
<td>Dispensing and Coating, Extrusion, Coating and Drying, Packaging</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Liquid- or Powder-filled Capsule</td>
<td>1</td>
<td>Granulation: Wet and Dry, Milling and Blending, Drying, Encapsulation and Packaging</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Compressed Tablet</td>
<td>1</td>
<td>Granulation: Wet and Dry, Milling and Blending, Drying, Compression and Packaging, Film Coating</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>
Other Key Documents

• USP <1115> Bioburden Control of Non-sterile Drug Substances and Products was published in the 2nd Supplement to USP37-NF32 July 2014.

• PDA TR No. 67 Exclusion of Objectionable Microorganisms from Non-Sterile Pharmaceuticals, Medical Devices and Cosmetics published October, 2014
Class Exercise

Breakout Session

- 2 groups
- 1 spokesperson per group
- 1 scribe per group
- Problem review: 15 minutes
- Report back: 2-3 minutes per group
Class Exercise

Application of risk assessment tools to the development of a film-coated compressed tablet.

• Where does this dosage form lie of the route of administration hierarchy?

• Which pharmaceutical ingredients would have the highest risk of microbial contamination?

• What unit manufacturing steps would led to an increase in bioburden? What are the critical control points?

• Would the product support the growth of microorganisms?

• What patient population may be more susceptible to microbial infection?
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
• Fluid-bed drying
• Tablet compression
• Tablet coating
• Packaging
• Distribution
Class Exercise

• Identify potential sources of risk of microbial contamination and describe how those risks would be mitigated.
Thanks for Your Attention

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