U.S. FOOD & DRUG ADMINISTRATION

Aging Operations: A US-FDA Perspective

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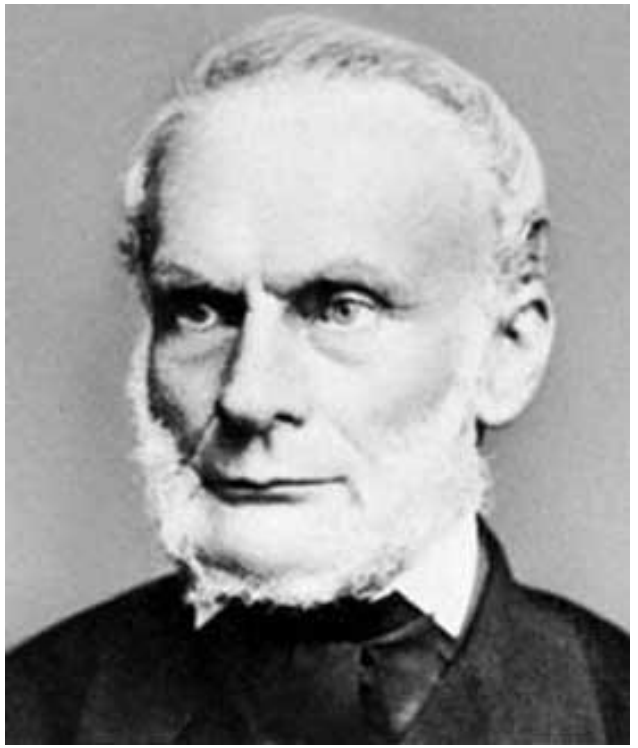
Rough Presentation Outline

- The Reality of Aging
- Aging Operations - Regulatory Expectations
- The Secret to a Long Life and Aging Gracefully
- Stuff You Need to Get Right (Even If You Know the Secret)
- Addressing an Emerging Area of Concern

What Does it Mean to be "Aging"?

The entropy of a system will always increase over time.



Why Do Some Age So Poorly?

Money?

Misconceptions About CGMP:

- A manufacturer meeting CGMP expectations now will meet all minimum standards in perpetuity by maintaining the status quo.
- Having submitted information in an application that was approved 20-30 years ago protects one from having to make feasible and valuable changes to a process.
- Something cannot be considered CGMP until it is widely adopted.

Quality Risk Management

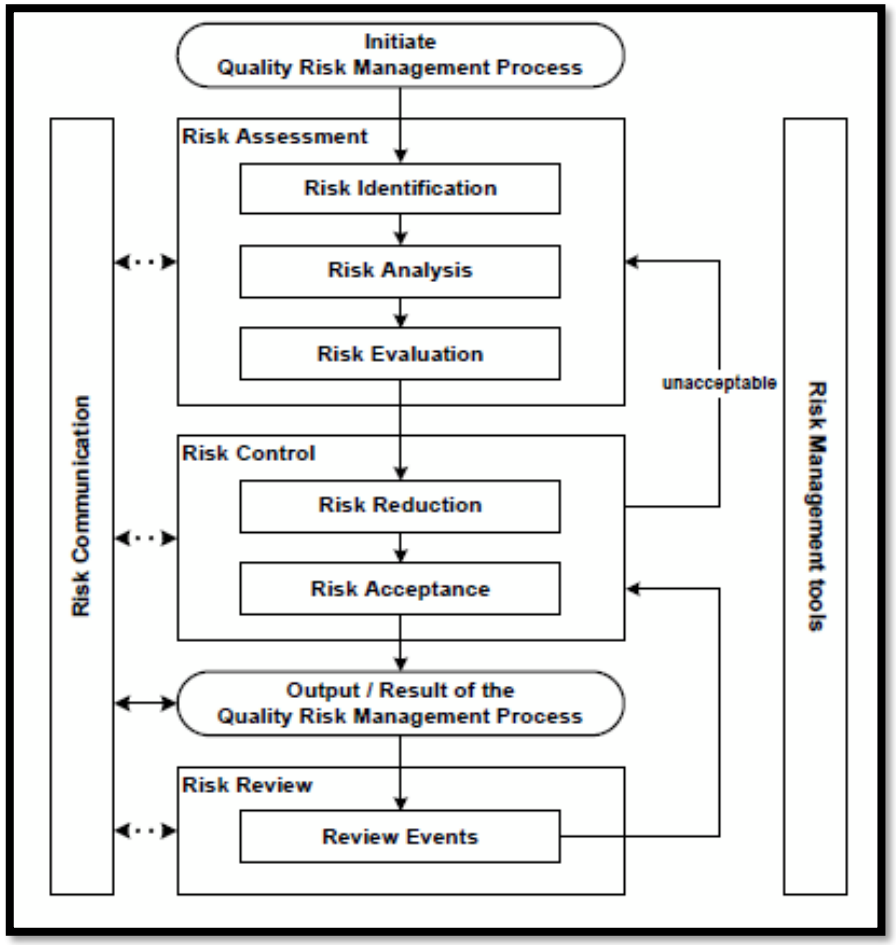
- Design
- Control
- Maintenance

Q9(R1) Quality Risk Management

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2023
ICH-Quality



Lifecycle Knowledge May Trigger Risk Review

- QRM includes “taking into account **new knowledge** and **experience**.”
- Lifecycle events can “impact the original quality risk management decision.”

ICH Q9(R1), Quality Risk Management
Published by ICH in January 2023

Lifecycle Knowledge May Trigger Risk Review – ICH Q9(R1)

"The interests of patients are served by use of QRM to proactively manage quality risks and ensure quality and availability of medicines. "

- *Lifecycle* factors that can affect quality and product availability, include the following:

  (1) manufacturing **process variation and state of control**;

  (2) manufacturing **facilities and equipment**;

  (3) oversight of **outsourced activities and suppliers.**

Operations Oversight
Critical Senior Management Role

- Senior management has a critical ongoing oversight role to ensure suitability of operational design, control, and maintenance.
- Leaders emphasize that everyone is responsible for assuring quality. This principle is an important one for both the leaders and those they lead.
- Senior managers have critical responsibility to allocate resources for production infrastructure upgrades if operations are deficient.

Management Decisions Create the *de facto* Culture

Management's daily decisions on myriad issues involving equipment, materials, maintenance, staff qualifications, supervision, process control, and investigations will ultimately determine the quality of the drugs that are shipped from a given facility.

Woodcock, J and M. Wosinska, Clinical Pharmacology & Therapeutics, "Economic and Technological Drivers of Generic Sterile Injectable Drug Shortage," Jan 2013

Critical Role of Subject Matter Experts

Are qualified SMEs routinely present on multi-disciplinary teams that make manufacturing design, control, and validation decisions?

For example, for sterile drug manufacturing processes, it is clear that microbiology SMEs contribute essential knowledge to enable sound judgments and effective risks management.

- **Design**: identifying hazards in aseptic operations; risk reduction options
- **Sanitary system** design & control (e.g., piping, sanitization, biofilm prevention)
- **Disinfection** selection, procedures, and validation

FDA Draft Guidance for Industry - Microbiological Quality Considerations in Non-sterile Drug Manufacturing

- Published September 2021
- Discusses product development considerations, risk assessments, and certain CGMP requirements that are particularly relevant to microbiological control in manufacturing operations for solid, semi-solid, and liquid non-sterile dosage forms

The Need for This Guidance

- Inspectional and assessment findings
- Review of complaints, adverse event reports, and recalls involving objectionable contamination of non-sterile dosage forms
  - This includes, but is not limited to, specific concerns regarding *Burkholderia cepacia* Complex (BCC) and its associated severe consumer harm

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Objectionable Microorganisms

"Microorganisms could be objectionable by virtue of their total numbers or their detrimental effect on the product or by their potential for causing illness in the persons ingesting them."

Principles of a Risk-Based Impact Assessment

- The approach necessary to prevent objectionable microorganisms will depend on the **risk** of microbiological contamination in the non-sterile drug (NSD), including:
  - the characteristics of the NSD (e.g., liquid vs. tablet)
  - the NSD **manufacturing process**
  - the impact of the **manufacturing environment**
- Well-designed and appropriately controlled manufacturing processes present fewer opportunities for introducing objectionable microorganisms

Manufacturing Elements – Water

- Water used as a component must be of appropriate quality for its intended uses in processing and formulation
- **Water purification systems must be well-designed and rigorously controlled and maintained**
  - proactive replacement of parts to prevent deterioration
  - routine monitoring to assure the system can consistently produce water meeting its predetermined quality characteristics
- Monitoring should incorporate appropriate action and alert limits and include **timely sampling** after key water processing steps and **equipment used in the water processing and delivery system, including all points-of-use**

Water Systems

- Water system control deviations can be difficult to detect due to sampling limitations
- **Proper water system design** and control, appropriate microbial action limits, and routine water quality testing are critical to assuring that microbial levels are below established limits, and that the water is free of objectionable microorganisms
- In addition to proper design and appropriate monitoring, manufacturers should have controls designed to prevent the introduction of objectionable microorganisms, as well as **procedures for cleaning, and maintenance**

Manufacturing Elements – Facilities and Equipment

- **Environment: Manufacturers must ensure that facilities, equipment, and environmental conditions are adequate to ensure control of air quality for manufacture**
- **Equipment: Bioburden should be limited through proper equipment design (e.g., vessels, piping), maintenance, cleaning, and sanitization**

Specific Example, FDA Advisory Notice

"**The FDA advises drug manufacturers of non-sterile, water-based drug products that *Burkholderia cepacia* complex (BCC or *B. cepacia*) continues to pose a risk of contamination.**[1], [2], [3] BCC is a group of gram-negative bacteria …. that has been linked to multiple instances of opportunistic infections.[4] For example, Paroex® Chlorhexidine was recalled in 2020 due to objectionable microbial contamination including the BCC species *B. lata*. **Inadequate design, control, or maintenance of pharmaceutical water systems have led to contamination with BCC and other water-borne opportunistic pathogens.**"

Draft Guidance Appendix: Case Study Examples of Microbiological Contamination of NSD Products; Impact on Product Quality and Manufacturing Process

- Case 1: Contamination of an oral solution with *Burkholderia cepacia* complex
- Case 2: Contamination of aqueous-based throat spray and liquid antacid with *Escherichia coli*
- Case 3: Contamination of moisturizing cream with *Pseudomonas* and *Staphylococcus*
- Case 4: Excessive contamination of a non-aqueous-based cream indicated for infants
- Case 5: Topical cream contaminated with *Enterobacter,* sp.
- Case 6: Alcohol antiseptics contaminated with *Bacillus cereus*
- Case 7: Contamination of an API with *Aspergillus*, sp. and *Enterobacter,* sp.

Take Home Messages

- Existence Leads to Aging
- Systems Tend Toward Disorder; You Must Work to Maintain Systems
- At Some Point, Maintenance Will Not Be Enough
- CGMP Means Incorporating Feasible and Valuable Changes
- Proper Design and Maintenance of Operations are Essential for Long, Healthy Lives
- Quality Risk Management, with Senior Management Support and Subject Matter Expert Input, are Essential for Proper Design and Maintenance of Operations
- Failures to Appropriately Design and Maintain Operations Lead to Loss of Control and Can Have Serious Patient and Consumer Impact
- Failures to Properly Design and Maintain Non-Sterile Drug Manufacturing Operations Have Led to Serious Adverse Events, Including Death

Thank You!

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