RISK BASED APPROACH TO GMP MANUFACTURING FACILITY DESIGN: THE FUTURE OF BIOPHARMA MANUFACTURING

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Risk Based Approach to GMP Manufacturing Facility Design
Introduction

> What is risk?
> What does it have to do with manufacturing?
> How do we identify and mitigate risk?
> How does it impact facility design?
What is risk?

> Risk
  A situation involving exposure to danger.

> Danger
  The possibility of suffering harm, or
  The possibility of something unwelcome or unpleasant.
Kinds of risk?

> Perceived
   An emotional interpretation of risk

> Real
   Fact driven interpretation of risk

Kinds of risk: Overt Risk

> Perceived
   A risky venture: High likelihood of death

> Real
   Less than driving a car (0.0007% vs. 0.0167%)
Kinds of risk: Hidden risk

> Perceived
  Fun, Scary, Safe Ride

> Real
  Highest risk of injury in Florida Theme Parks*

*Orlando Sentinel May 21, 2018

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Kinds of risk: Outcomes

> Automobiles
  Fatalities: 1.12 per 100 million VMT
  2017: 40,100 fatalities in US
  More injuries than deaths

> Planes
  Fatalities: 0.25 per 100 million flights
  2017: Zero fatalities in US
  More deaths than injuries

*Orlando Sentinel May 21, 2018
Kinds of risk:
Perception

> Our ability to perceive risk is colored by our concerns for type and amount of harm that might happen, as well as our individual experiences with that risk

> Often disconnected from real risk probability and outcomes

What is Risk?

Formal Definition:
• ISO 31000 defines Risk as:
  “the effect of uncertainty on objectives…”

Working Definition:
• Risk is:
  A measure of the importance of an event that includes both the factors of Impact and Probability
Biological Risk

- Living biological products - inherent variability of cell populations in raw material and final product
  - Source of cells, inter-individual variability
  - Potential for adventitious agent contamination, inability to “sterilize” the final product
- Complex scientific procedures
  - Greater risk of untoward events
- Novel uses of cells and materials
  - Difficult to predict likelihood of adverse outcomes

Regulation Reflects the Evolving Nature of Cell-, Gene- and Tissue-Based Therapies

- Cell therapy, gene therapy, and tissue-engineered products are complex living biologics, and are being developed in novel, evolving ways. Regulation of these products commonly reflects their novel, diverse nature.
- Regulations set a framework of criteria that must be met.
  - Safety, identity, purity, potency, and clinical efficacy
- Regulatory agencies, in general, follow a science-driven, risk-based approach in evaluating whether and how these criteria have been met.
  - Products that present greater risk of adverse clinical outcome require more and better control, and hence more stringent regulation and oversight.
What Can I Do About Risk?

Avoid – Don’t do it

Reduce (Mitigate) – Make it better

Transfer – Make Someone else do it

Accept – Live with it

Examples of Risk
Examples of Risk
Why do we need Risk Management?

- Standards and Regulations are limited
  - Regulations are slow to change and not flexible
  - FDA Guidance doesn’t evolve as quickly as science
  - Appendix K Recombinant DNA guidance is old
- Owners and A&E teams have fiduciary responsibilities
  - To protect employees
  - To protect the community
  - To protect patients
- The stakes are high - Failure is not an option
Why do we need Risk Management?

- We need tools that are **strong** enough to assure quality... yet **flexible** to evolve with technology evolving risks.
  - Evaluate alternatives
  - Look for weaknesses
  - Look for opportunities
  - Balance conflicting needs

NO Cookbooks!

Balancing the Needs

1. Containment - Keeping things in
   a. Employee Safety
   b. Separation of systems
   c. Environmental Safety
2. Security – Keeping things out
   a. Contaminant reduction
   b. 'Sterility'

“Security and containment often oppose one another; Security is based on the concept of keeping contaminants out, whereas containment is based on the concept of keeping organisms and byproducts in.”
What Can I Do About Risk?

• We all have to live with risk:
  - Decide how much
  - Learn to detect
  - Continually re-evaluate

Acceptable Risk?

• We accept risks of injury, even death, every day...
  - Driving to this conference >30,000 deaths/yr (US)
  - Flying 500-1000 deaths/yr
  - Taking a shower >5,000 deaths/yr
  - Shaking the hand of a stranger
    “Hi my name is patient zero...”
• Risk Management helps us to mitigate and accept risk
What is Risk Management?

Formal Definition:
• Risk management is:
  (Risk) ... followed by coordinated and economical application of resources to minimize, monitor, and control the probability and/or impact of unfortunate events...

Working Definition:
• Risk management is:
  A method for identifying potential problems and prioritizing responses across a lifecycle

What ISN’T Risk Management?

What risk management is not for...
What is Risk Management?

> Our ability to perceive risk is colored by our concerns for type and amount of harm that might happen, as well as our individual experiences with that risk.

> Often disconnected from real risk probability and outcomes.

> Risk Management aligns experiences and perceptions with reality and outcomes.

Risk Management is a multi-step process:

- Identifying Risks (what can go wrong)
- Analyzing Risks (what causes them?)
- Evaluating Risks (how bad are they?)
- Controlling Risks (mitigating risk)
- Reviewing Risks (risk iterations)
- Accepting Risks (residual risk)
Risk Management Tools – ICH Q9

What is Q9?

1. It provides principles and a framework for decision making
2. It is a “guidance not an SOP
3. It supports science-based decision making
4. Facilitates communication and transparency
5. Tools in Q9

Risk Management

Can be Quantitative (often used in engineering)
- Airborne challenge < 10 organisms/m³
- Filtration array with 2 failures, 99.00% efficient
- Post filtration 1 organism/ 10 m³

Or Qualitative (often used in Facility Design)
- SEVERITY of the failure = Low
- Probability of OCCURRENCE of failure = Medium
- The possibility of NON-DETECTION = High
Risk Management Tools

Methods Used in Assessing Risk
- Preliminary/Process Hazard Analysis (PHA)
- Hazard and Operability Studies (HAZOPS)
- Fault Tree Analysis (FTA)
- Hazard Analysis and Critical Controls Points (HACCP)
- Failure Mode and Effects Analysis (FMEA)

Risk Analysis Methodologies

HAZOP

- A systematic, critical examination of the process and engineering intentions to assess the hazard potential that arise from deviation in design specifications.
- A Nodal analysis of process system or unit using fixed taxonomy (guidewords): No/Not, More/Less, As Well As, Part of Reverse, and Other Than.
- Nodes are usually derived from schematic drawings
- Time and resource consuming effort
- Very Compatable with FMEA
Hazard Analysis and Critical Control Points (HACCP)

- Developed by food microbiologists
- A Legal requirement in the Food Industry
- Emphasis on ...
  - Design
  - Control Mechanisms
- Systematic assessment of ALL systems
- Identification of those systems and components which are CRITICAL to safety

Fault Tree Analysis (FTA)

- Used to identify “root causes” of a failure
- Evaluates system (or sub-system) one at a time
- Can combine multiple causes by working on identifying causal chains
- Can be used with probabilities for quantitative assessment
- Results are represented pictorially in the form of a tree of fault modes
- Fault modes are described with logical operators (AND, OR, etc.)
Failure Mode and Effects Analysis (FMEA)

- FMEA/FMECA
- Most commonly used risk analysis technique
- Basis of many other risk assessment techniques
- Combines well with other techniques
  - Ishikawa for risk identification
  - HazOp style fixed taxonomy
  - HACCP for identification of control points
  - FTA to identify components that cause failure

- Roots in engineering but can easily be applied across the industries

- Involves calculation of a: RISK PRIORITY NUMBER derived from a combination of:
  - The SEVERITY of the consequence of failure S
  - The probability of OCCURRENCE of failure O
  - The probability of NON-DETECTION of the failure D

\[ \text{RPN} = S \times O \times D \]
FMEA – How to do it

Define your scale before you start!

Severity
- 5 = Loss of containment
- 3 = Transient upset
- 1 = No impact

Occurrence
- 5 = Very frequent (≥ monthly)
- 3 = Frequent (≤ annually)
- 1 = Infrequent (≤ 1/5 yr)

Non-Detection
- 5 = Not detectable
- 3 = Indirectly detectable (delayed)
- 1 = Self-evident

“Failure Mode”
- What does a thing do?
- What if it stops doing it, what happens?

“and Effects”
- Look for the Effects, not cause,
- Will other equipment fail too?
- do critical parameters get impacted?
  - Safety, Containment, Required Conditions?
FMEA – How to do it

“Analysis”
- Decide if the failure is important before looking at how it fails
- Score using the SxOxD = RPN
- If the failure is “high risk”
  - Then Drill down to contributing factors.
  - Don’t get caught in the weeds, the contributing factors are only there to help with determining probability and mitigation planning.

FMEA – How to do it

If it’s Critical... (An Example)

Failure Causes for an Air Handler fan
- Delivering Air
  - None
  - Belt Breaks
  - Fuse Blows
  - Bearings Fail
  - Control Failure
  - Exhaust Interlock
Other Lessons Learned on FMEA

• Risk Priority Number (RPN)
  - The absolute number is unimportant
  - RPN allows risks to be ranked
  - Allows action to be prioritized
  - Provides justifiable basis for decision making... including doing nothing!
  - Documented so that history is available
  - Evaluate before and after mitigations – quantifies mitigation effectiveness

Document Your Assessment

<table>
<thead>
<tr>
<th>System Component</th>
<th>Hazard (Failure mode)</th>
<th>S</th>
<th>O</th>
<th>D</th>
<th>RPN</th>
<th>Notes (inc. assumptions)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

If It’s Not Written Down, It Doesn’t Exist!
When performing any risk analysis, take advantage of your problems!

- Deviations, mistakes, and failures are valuable indicators of process weaknesses, and should be embraced.
- Use deviation reports as tools for process improvement.

*Productive mistake-making!*

HOW DOES THE RISK ASSESSMENT SUPPORT DESIGN?

- Design Intent
- Hidden Risks
- Over Design
- Design Initiatives
Design Intent

> Coordinating Operations with Design
> Accepting Realities of Risk
> Setting Priorities and Principles

Design Intent

Coordinating Operations with Design

Form Follows Function:

> The URS
  – What the Users need
> Programming:
  – Mapping space requirements and adjacencies
> Test Fits
  – Concept plans
> A risk-based design is only as good as the description of the needs and the operation plans
Design Intent
Accepting Realities of Risk

> Bad things happen to good people
> The “It can’t happen here” syndrome
  – Low incident
  – Luck!
> Better to design to avoid potential risks than to trigger avoidable investigations or shutdowns

Design Intent
Setting Priorities and Principles to Reduce Risk
Investments in Time to Avoid Future Problems
> Design Priorities
  – Time, money, quality, other?
> Design Principles - List of procedures and operations based upon:
  – Regulatory approvals
  – Corporate standards
  – Corporate culture
  – History
  – Industry minimum standards
Design Intent
Setting Priorities and Principles to Reduce Risk

> Design Principals

### OPERATING PRINCIPLES FOR GMP FACILITY

<table>
<thead>
<tr>
<th>ITEM</th>
<th>TOPIC</th>
<th>CATEGORY</th>
<th>SUB-CATEGORY</th>
<th>PRINCIPLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PPE</td>
<td>Donning</td>
<td>ISO 8</td>
<td>Ready wearing scrubs and plant shoes; Don head cover, face cover (mask/glasses or shield), shoe cover, gloves, &amp; gown (beard cover as required)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ISO 7 &amp; 6</td>
<td>Don second gloves, second shoe cover (bootees), body cover;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Doffing</td>
<td>Must remove when exiting facility and re-gown to re-enter; no change needed between ISO 8 rooms</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ISO 7 &amp; 6</td>
<td>Must remove when exiting room and re-gown to enter or re-enter; Change needed between ISO 7/6 rooms</td>
</tr>
<tr>
<td>2</td>
<td>Materials</td>
<td>Single Use</td>
<td>All</td>
<td>All materials will be single use unless authorized by Facility Director; Re-use materials require approved SOP for use and sanitization between uses</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Washing/Sanitization</td>
<td>All</td>
<td>Washing and sanitization of new or re usable materials will be performed outside of the facility (TBD)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Entry</td>
<td>Facility</td>
<td>All incoming goods will enter the facility through an airlock after surface chemical decontamination with approved procedures</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Room</td>
<td>Facility</td>
<td>All incoming goods will enter process rooms through an airlock after surface chemical decontamination with approved procedures</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Exit</td>
<td>Facility</td>
<td>All outgoing goods will exit the facility to waste or through the equipment air lock in a secondary container after surface chemical decontamination with approved procedures</td>
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<td>Facility</td>
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<td></td>
<td>Room</td>
<td>Facility</td>
<td>High risk rooms will have a separate MAL for decontamination process</td>
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### Hidden Risks

> Design changes
> Removing too much
> Ignoring principles
Hidden Risks
Design Improvements

> Adding too much creates risk
> ‘Better’ is the enemy of ‘Best’
  – Design improvements should fit into all programming elements and requirements
  – Improvements should be re-evaluated in the risk assessment
  – Should not be back door approach for ideas already rejected
  – Should not introduce new compromises or unnecessary risks

Hidden Risks
Removing Too Much Creates Risk

> Value Engineering
  – Cost vs. Value
  – Not all cost reductions are equal
> Over simplification
  – ‘Easier’ to operate or repair is good as long as function and validation is preserved
  – Having mechanical standards is helpful
> Convenience
  – Be careful that convenience features don’t change risk profile or compliance
Hidden Risks
Ignoring Principles Creates Risk

> Principles support uniformity of operations
  – Less errors and deviations
  – Design remains coordinated with operations
> Exceptions are hard to manage and usually harder to justify to regulators

Over Design

> Space consolidation
> Corridors
> AHU strategies
> Emotional Needs vs. Function
Over Design
Space Consolidation: Savings Without Added Risk

> Core Laboratories
  – Centralized services providing economy of Scale
> Combined airlocks based upon function:
  Reduced air lock space
> Suites vs. individual rooms
  – More efficient mechanical systems
  – Product separation principles

Over Design
Corridors: Construction Savings Without Adding Risk

> Down grading corridors
  – Corridors make up a large percentage of program area
  – Reduced mechanical requirements: CapEx and OpEx savings
  – Reduced architectural finishes on walls and ceilings
Over Design
AHU strategies: Energy Savings Without Adding Risk

> Air Recirculation

Over Design
AHU strategies: Zoning to Balance Risk and Function

> Based upon risk assessment and product separation strategy
Over Design
Emotional Needs: Adding Risk Without Benefit

> Emotional Needs: The “I Want” Syndrome
  – Leads to excess functionality
  – Uncertainty of function and design
  – Strong personalities

Design Initiatives to Manage Risk

> Convertible Suites
> Design Flexibility
> Future Proofing
Design Initiatives
Convertible Suites

> Design Flexibility
  – Modules sized and designed to have two or more functions
  – Strategy to switch between functions built into design
  – Strategy manages risk and constructability

Design Initiatives
Design Flexibility to Avoid Risk

> No ‘Monuments’
  – Avoid immobile objects when possible
  – Place mechanical shafts off to side

> Mobile equipment
  – Easier to clean around
  – Cheaper and faster to make changes

> Strategic utility panels
  – Simplifies ability to add future technologies
  – Leave space and access for new utilities
Design Initiatives
Future Proofing

> Anticipating future needs
  – Can’t foresee new technologies
  – Can design facilities to accommodate change
> Creating options
> Goal is to manage uncertainty and develop strategies that will minimize risk associated with change

Risk Based Approach to GMP Manufacturing Facility Design
Summary

> Risk:
  – Real or Perceived
  – Overt or Hidden
> Impact on manufacturing
  – Always present to some degree
> Identification and mitigation of risk
  – Risk Assessment
> Impact on facility design
  – Better designs through the risk assessment process
QUESTIONS?