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

Jim Levin
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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?

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

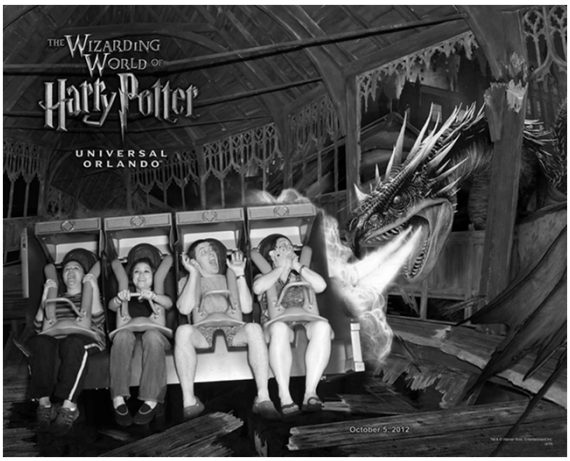
Less than driving a car (0.0007% vs. 0.0167%)

Kinds of risk:
Hidden risk

> Perceived
Fun, Scary, Safe Ride

> Real
Highest risk of injury in Florida Theme Parks*

*Orlando Sentinel May 21, 2018



Kinds of risk:
Outcomes

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

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

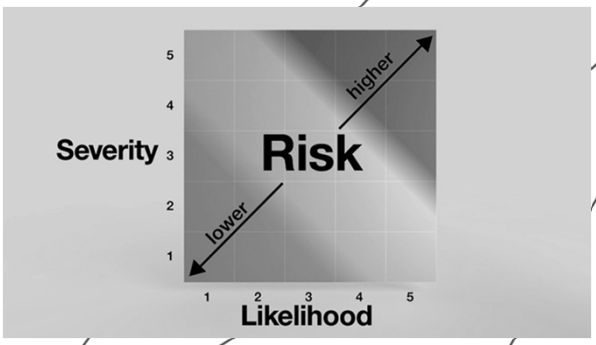
Examples of Risk

Examples of Risk

Examples of Risk

RISK MANAGEMENT

THE RISK ASSESSMENT



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

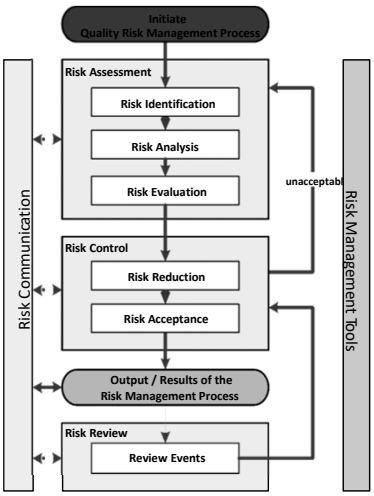
> Often disconnected from real risk probability and outcomes

> Risk Management aligns experiences and perceptions with reality and outcomes

What is Risk Management?

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/m^3
- Filtration array with 2 failures, 99.00% efficient
- Post filtration 1 organism/ 10 m^3

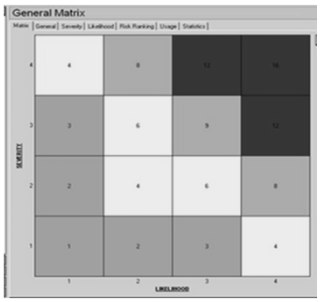
Or Qualitative (often used in Facility Design)

- 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

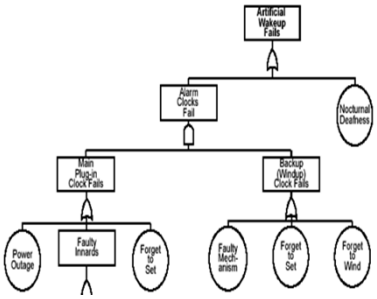
- A systematic, critical examination of the process and engineering intentions to assess the hazard potential that arise from deviation in design specifications.
- A Nodal analysis of process system or unit using fixed taxonomy (guidewords): No/Not, More/Less, As Well As, Part of Reverse, and Other Than.
- 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

Failure Mode and Effects Analysis (FMEA)

- 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

$$RPN = S \times O \times D$$

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

FMEA – How to do it

"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

System Component	Hazard (Failure mode)	S	O	D	RPN	Notes (inc. assumptions)

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?

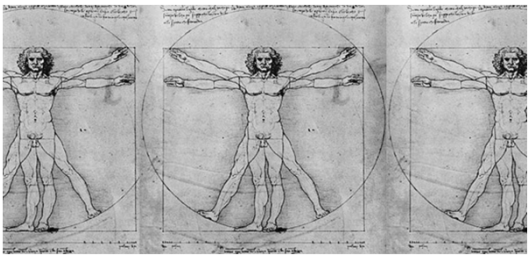
DESIGN INTENT
HIDDEN RISKS
OVER DESIGN
DESIGN INITIATIVES

Design Intent

> Coordinating Operations with Design

> Accepting Realities of Risk

> Setting Priorities and Principles



Design Intent

Coordinating Operations with Design

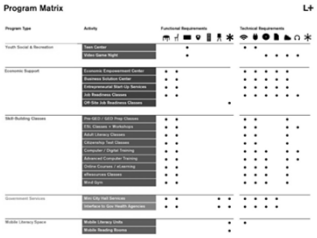
Form Follows Function:

> 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



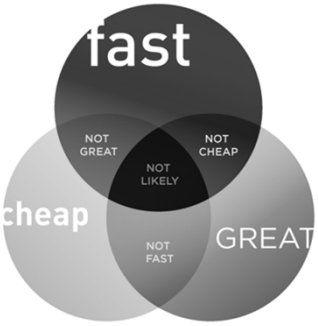
Design Intent
Accepting Realities of Risk

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

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

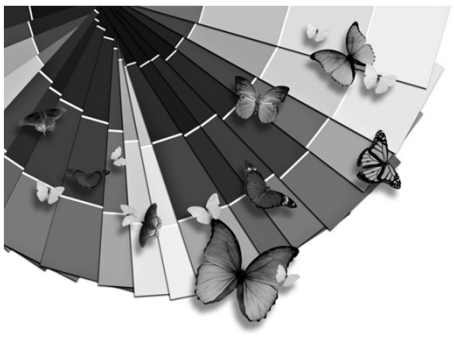
> Value Engineering
  – Cost vs. Value
  – Not all cost reductions are equal
> Over simplification
  – 'Easier' to operate or repair is good as long as function and validation is preserved
  – Having mechanical standards is helpful
> Convenience
  – Be careful that convenience features don't change risk 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

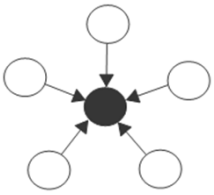
> Space consolidation
> Corridors
> AHU strategies
> Emotional Needs vs. Function

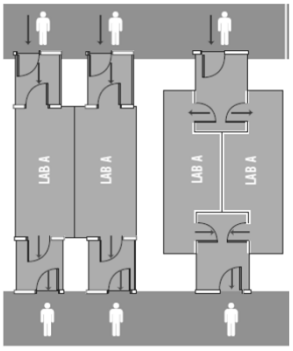


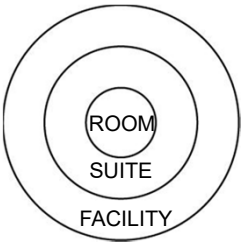
Over Design

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



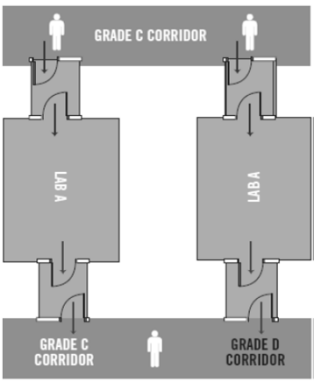




Over Design

Corridors: Construction Savings Without Adding Risk

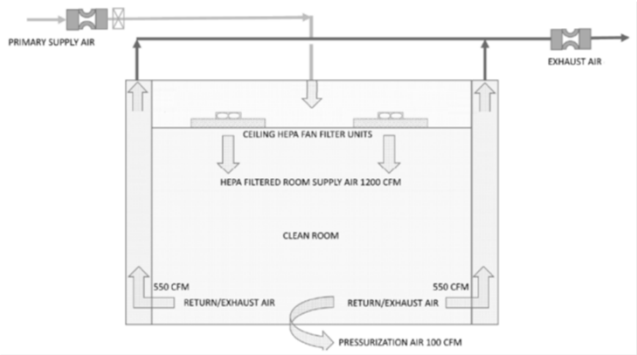
> Down grading corridors
  – Corridors make up a large percentage of program area
  – Reduced mechanical requirements: CapEx and OpEx savings
  – Reduced architectural finishes on walls and ceilings

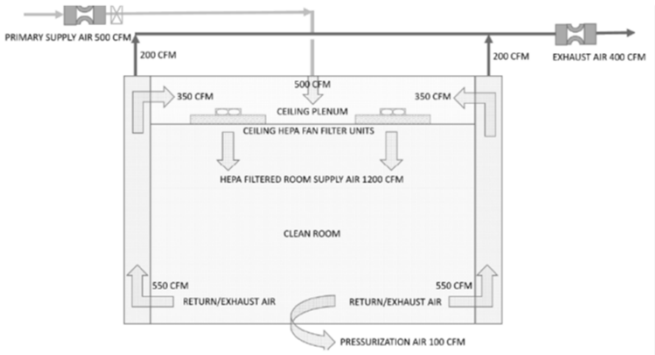


Over Design

AHU strategies: Energy Savings Without Adding Risk

> Air Recirculation

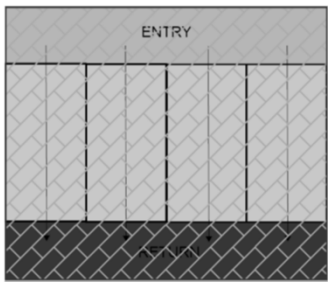




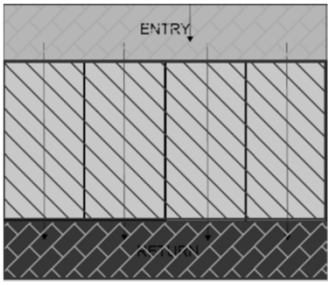
Over Design

AHU strategies: Zoning to Balance Risk and Function

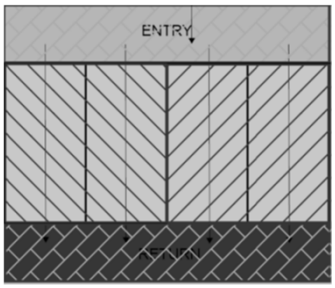
> Based upon risk assessment and product separation strategy



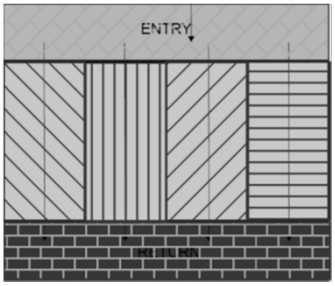
1 Zone



2 Zones



4 Zones



6 Zones

Over Design
Emotional Needs: Adding Risk Without Benefit

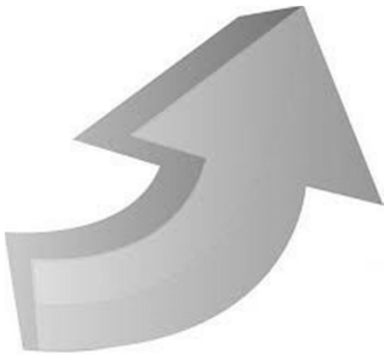
> Emotional Needs: The "I Want" Syndrome
  – Leads to excess functionality
  – Uncertainty of function and design
  – Strong personalities

Design Initiatives to Manage Risk

> Convertible Suites

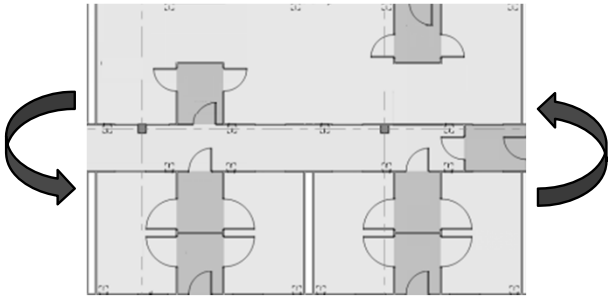
> Design Flexibility

> 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 associate 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?