

Advanced GMP Workshops 2017

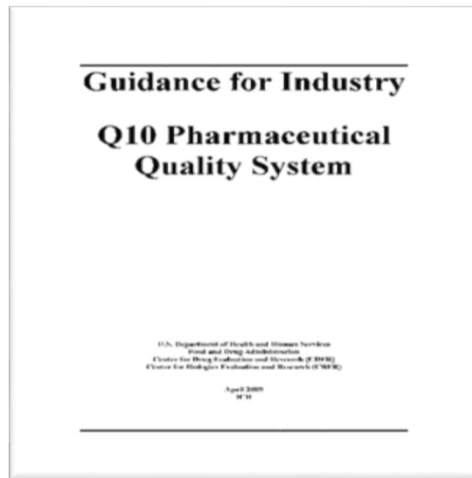
*Quality Issues and impact on Aseptic
Processing*

Advanced GMP Workshops 2017

- *Examine regulatory expectations for sterile products*
- *Discuss common quality observations in sterile production*

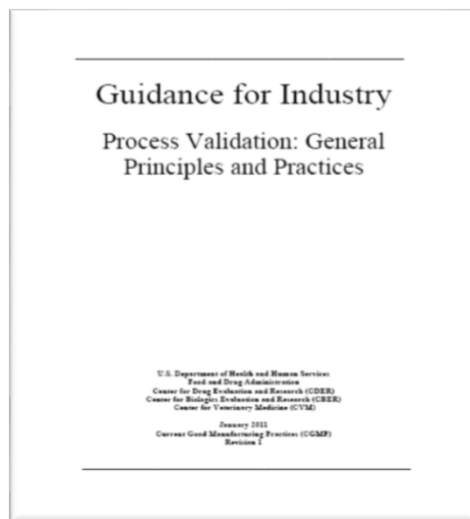


Advanced GMP Workshops 2017



ICH Q10 Definition of State of Control

A condition in which ***the set of controls consistently*** provides assurance of continued process performance and product quality. (ICH Q10)



FDA Process Validation Guidance on State of Control

“After establishing and confirming the process, ***manufacturers must maintain the process in a state of control over the life of the process***, even as materials, equipment, production environment, personnel, and manufacturing procedures change.”



State of Control

- Is a daily minute by every minute State
- Have you ever had days like this?

<https://youtu.be/NkQ58l53mjk?t=1>



State of Control - Validation

- “The collection and ***evaluation*** of data, from the process design stage through commercial production, which establishes ***scientific evidence*** that a process is ***capable of consistently*** delivering quality product.”
- In other words, a firm is responsible for ***lifecycle evaluation*** of the manufacturing operation

❖ Guidance for Industry Process Validation -
General Principles and Practices, 2011

State of Control

“...the explosion occurred at about 10 p.m. CST on Tuesday night 4/20/10, and came without warning”,

Transocean executive –
NY Times 4/21/10





State of Control

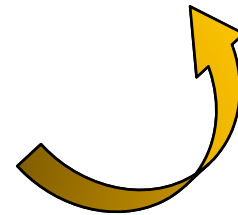
- In the *9/8/10 Horizon Accident Investigation Report Executive Summary - Appendix T -*

the report presents a “Comparison of Events with Relevant Transocean Well Control Policies, Practices and Procedures”, that describes each contactors roles and responsibilities e.g., “*Under the terms of the Contract*”, which briefly delineates who does what and why.

State of Control

- Transocean, the rig's owner, designates the offshore installation manager as the top official **when a rig is connected to an oil well**, as was the Deepwater Horizon.

Note for me...what the heck does this mean



- But international safety regulations place a captain in charge during a crisis. As panic ensued after the rig caught fire, witnesses have testified, questions emerged about **who should activate** vital emergency equipment and call to abandon ship.
- Chairman of the panel, the Coast Guard, concluded, **"Everybody in charge, nobody in charge."**

State of Control - In Oil Inquiry, Panel Sees No Single Smoking Gun

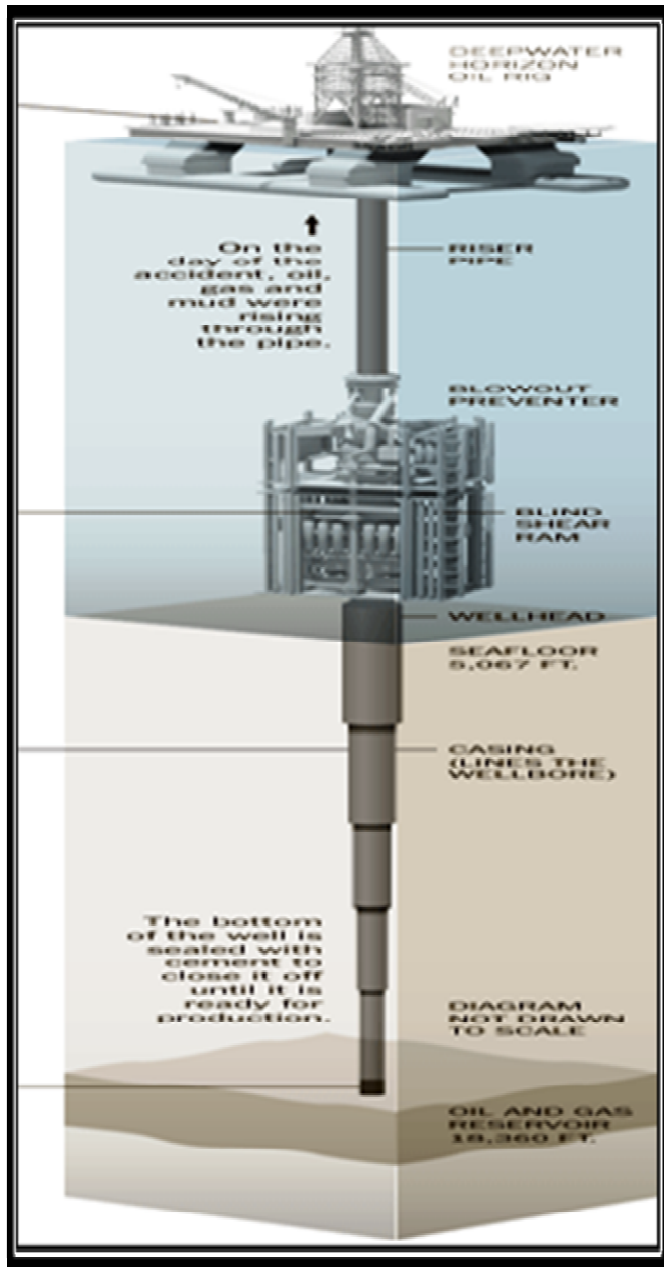
- More than four months after the Deepwater Horizon oil rig explosion, there appears to be ***no single smoking gun*** that implicates one person or company in the disaster. Instead, ***several missteps and oversights by the crew*** are being explored by federal investigators as possible triggers of the emergency.

8/27/10 - New York Times

Deepwater Horizon Accident Investigation Report



Executive Summary – 9/8/10



“The team did not identify any single action or inaction that caused this accident. Rather a complex and interlinked series of

- ✓ mechanical failures,
- ✓ human judgments,
- ✓ engineering design,
- ✓ operational implementation and
- ✓ team interfaces came together
- ✓ to allow the initiation and escalation of the accident.

Multiple working team and circumstances were involved overtime.”



Root Cause Analysis?

- “I don’t think we’ve truly gotten to the root causes,” a lawyer from a company that was contracted by BP to provide certain equipment in the well.
- “There are still more questions than answers.”

 *Published August 27, 2010*

Root Cause Analysis?

- Who was in charge of the rig, the captain or the offshore installation manager?
- It seems clear that a work crew would be able to identify its own boss.
- But witnesses have given conflicting answers about which of two senior officials was in command of the rig during the emergency.



A humble note on leadership

“Leadership is essential to establish and maintain a company wide commitment to quality and for the performance of the pharmaceutical quality system.”

 Q10 Pharmaceutical Quality Systems
ICH Guidance, May 2007

State of Control

Putting out fires is not improvement of the process

- W. Edwards Deming





Periodically Assess Process Capability and Variability

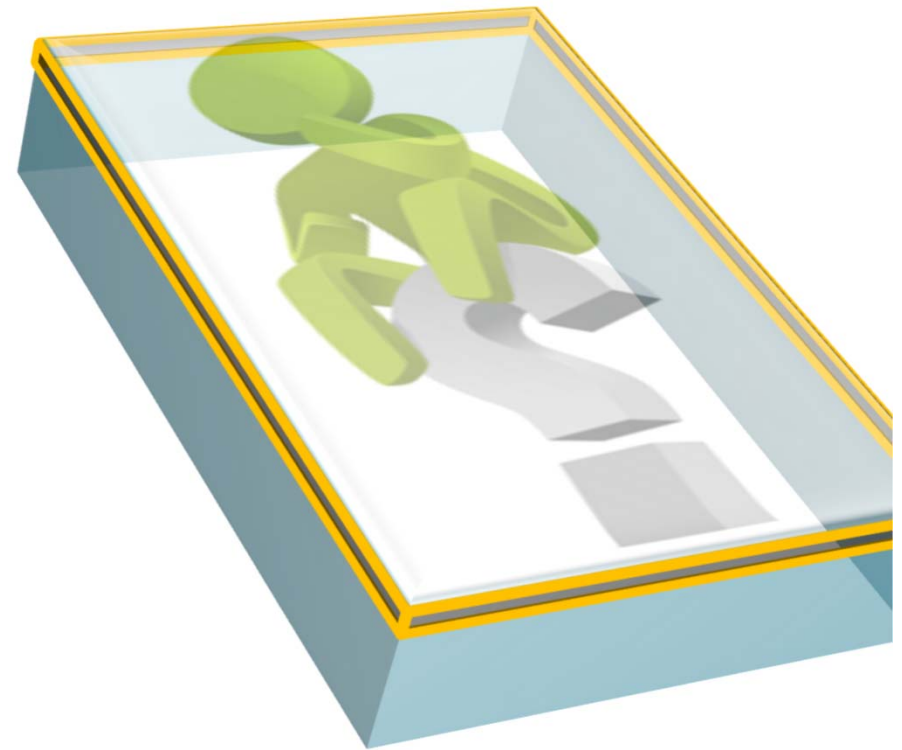
“We recommend continued monitoring and sampling of process parameters and quality attributes at the level established during the process qualification stage until

- ✓ **sufficient data are available to generate significant variability estimates....**
- ✓ **Process variability should be periodically assessed and monitoring adjusted accordingly.”**

❖ Guidance for Industry Process Validation -
General Principles and Practices, 2011

Easy words to say, which can be a bit of a challenge at times

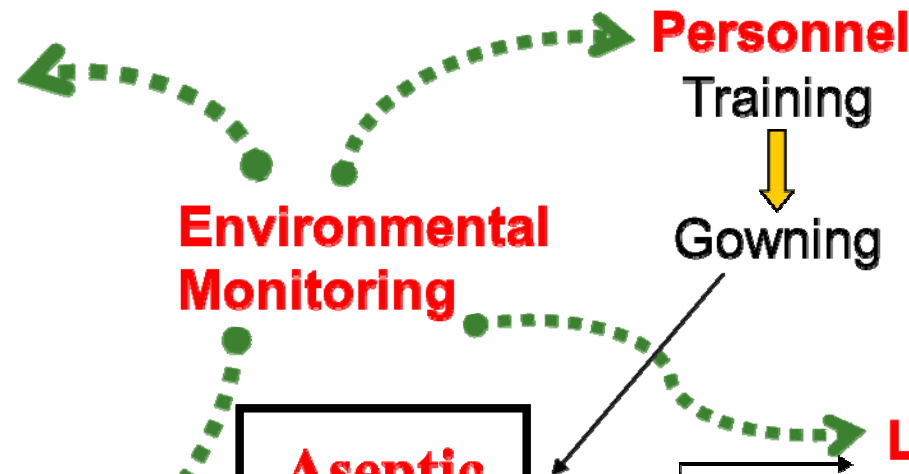
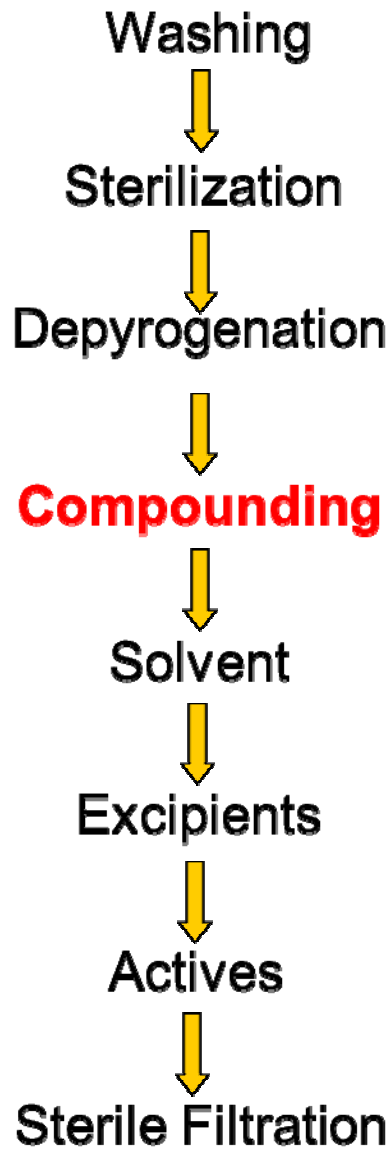
- “It is very difficult for an organization to see the truth about itself.
- those inside a box can seldom see what is happening within it.
- it usually takes someone looking from the outside in to produce useful evaluations.”



➤ Management *f-Laws how organizations really work*
Triarchy Press, 2007- Russell L. Ackoff

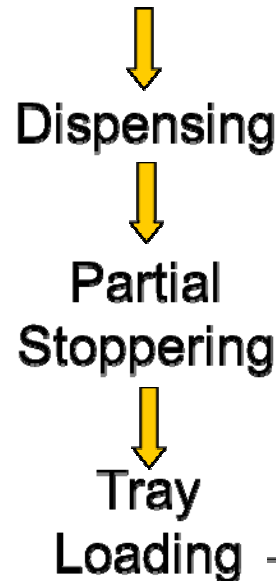
~ a Convergence of well orchestrated activities ~

Component & Equip Preparation

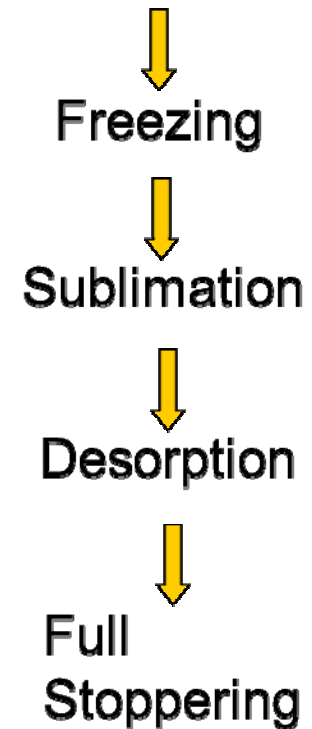


Flow of personnel & materials

Aseptic Filling



Lyophilization



Key Information for Quality Risk Management – May Trigger Risk Review or CAPA

- Non-conformances, discrepancies, deviations, failures, recalls
- Product Quality Data
- Process monitoring results *e.g., trend analyses from process performance and product quality monitoring*
- Equipment or Facility issues
- Raw Material Issues
- Regulatory Findings (local or at another site)
- Audits and self-inspections
- Complaints>Returns
- Stability Testing results

Getting to Root Causes

Are the firm's Investigations adequate?



- A large number of recent manufacturing failures can be traced to failures in the firm's **quality system**. In some cases,
 - ✓ the quality system ignored or **failed to follow-up on customer complaints**.
 - ✓ multiple repeated deviations were **treated as separate incidents**, rather than an **obvious trend**.
 - ✓ Another reoccurring theme has been investigations **"to nowhere"** ... These end with no additional understanding or insight into why the problem may have occurred and thus no hope for prevention.
- All of these failures suggest a quality management system that is **insufficiently empowered** or **resourced** to adequately carry out its essential functions.

Risk Management: are we connecting the *right dots*?



EU Chapter 1 – Pharmaceutical Quality Systems

Revision 3, effective date, January 31, 2013

Reasons for changes - Amendments to the text have been made in order to align with the concepts and terminology described in the ICH Q10 tripartite guideline on Pharmaceutical Quality Systems. The title of the chapter was also changed accordingly. Example:

- 1.4(A)(xiv): ***An appropriate level of root cause analysis should be applied*** during the investigation of deviations, suspected product defects and other problems.
- This can be determined using ***Quality Risk Management*** principles. In cases where the true root cause(s) of the issue cannot be determined, consideration should be given to identifying the most likely root cause(s) and to addressing those.

EU Chapter 1 – Pharmaceutical Quality Systems

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- Where **human error** is suspected or identified as the cause, this should be justified having taken care to ensure that **process, procedural or system-based** errors or problems have not been overlooked, if present.
- Appropriate corrective actions and/or preventative actions (**CAPAs**) **should be identified** and taken in response to investigations. **The effectiveness of such actions** should be monitored and assessed, in line with Quality Risk Management principles.



Continual Improvement - Science & Risk-Based

- Quality system elements and management role to allow for “use of ***science and risk-based*** approaches at each lifecycle stage, thereby promoting continual ***improvement*** across the **entire** product lifecycle.”
- ***QRM*** is part of the PQS and includes “a proactive approach to identifying, ***scientifically evaluating, and controlling potential risks*** to quality. It facilitates continual improvement of ***process performance and product quality*** throughout the product lifecycle.”
 - ❖ International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use - *ICH Q10*



Another brief note on leadership

- “Risk management, encourages proactive rather than reactive, management of product processing and is a means to an end, not an end itself.
- Rigorous thinking is involved with logical, systematic and science-based approaches to improve the effectiveness and efficiency of decision-making.
- The goals of a quality risk management program should be to better understand the process and improve the process, thereby assuring patient safety.”

❖ “Quality Risk Management for Aseptic Processing” –
PDA Technical Report #22, Vol.62, No. S-1, 2008

Are the Facility and Process Suitable?

- Current facilities have been built *“using technologies and processes from the 1950s and 1960s”*
 - ✓ Inefficient
 - ✓ Not always capable
- *“A more highly skilled manufacturing organization will be required to deal with the new technologies; however the improved automation and process control should bring staff [FTE] cost savings.”*

❖ *ILF GPS Document, Published by ISPE, May 2012*



Regulatory concerns – Aging Facilities

- A review of inspection reports for key facilities suggests that some facilities at the heart of current drug shortages have been in operation continually since the 1960s.
- The reports suggest that certain manufacturing lines have undergone only limited upgrades during that time...Such ***aging facilities require upgrades...***
- ❖ Woodcock, J. and Wosinska, M., Clinical Pharmacology & Therapeutics, “Economic and Technological Drivers of Generic Sterile Injectable Drug Shortage,” Jan 2013



Regulatory concerns – Modernization

Although *contemporary facilities are highly automated and use isolators and other separation technologies to protect the processing line from contamination risks,*

- older facilities typically include processing lines and facility layouts that are less effective at mitigating the various operational variables that pose risks to product sterility. If the equipment is not well designed or is poorly maintained, repeated or extensive manual interventions often occur due to mechanical problems.

When production line operators perform manual activities near an insufficiently protected product, they raise the risk of microbial contamination.

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

Mitigate Risk - Symptoms of Deficient Facilities and Processes

- Many processing lines require ***frequent starts and stops*** to correct problems and to pull samples (Tablet, Aseptic Processing Lines)
- ***Old Manufacturing Platforms*** (antiquated facilities, inefficient/unstable processes)
- ***Unpredictable manufacturing*** can lead to quality problems, defects, and supply shortfalls
- Many firms ***do not take advantage of contemporary technology***
- ***Open vs. Closed*** Processes (Also, Unit Operations vs. Integrated)
- ***Manually Intensive*** Operations vs. Automation
- As a result, ***Human Error still very prominent root cause...***

Consider your operations

Old Paradigm
Manually intensive operation - VS -

21st Century Paradigm –
Manufacturing changes that remove direct
human-machine interaction



Management Responsibility

Suitable Manufacturing Facilities and Processes

- Inadequate manufacturing capability is a frequent cause of drug defects and critical drug supply shortfalls, for example;
 - ✓ ISPE's industry survey cited lyophilization and sterile manufacturing as two areas in need of improvement.

- “Some...inspections have found operations with antiquated or obsolete facility or process elements, and operations with high defect rates in violation of cGMP. These operations are receiving higher focus, while manufacturing operations that have been upgraded and are more dependable have been deemphasized.”

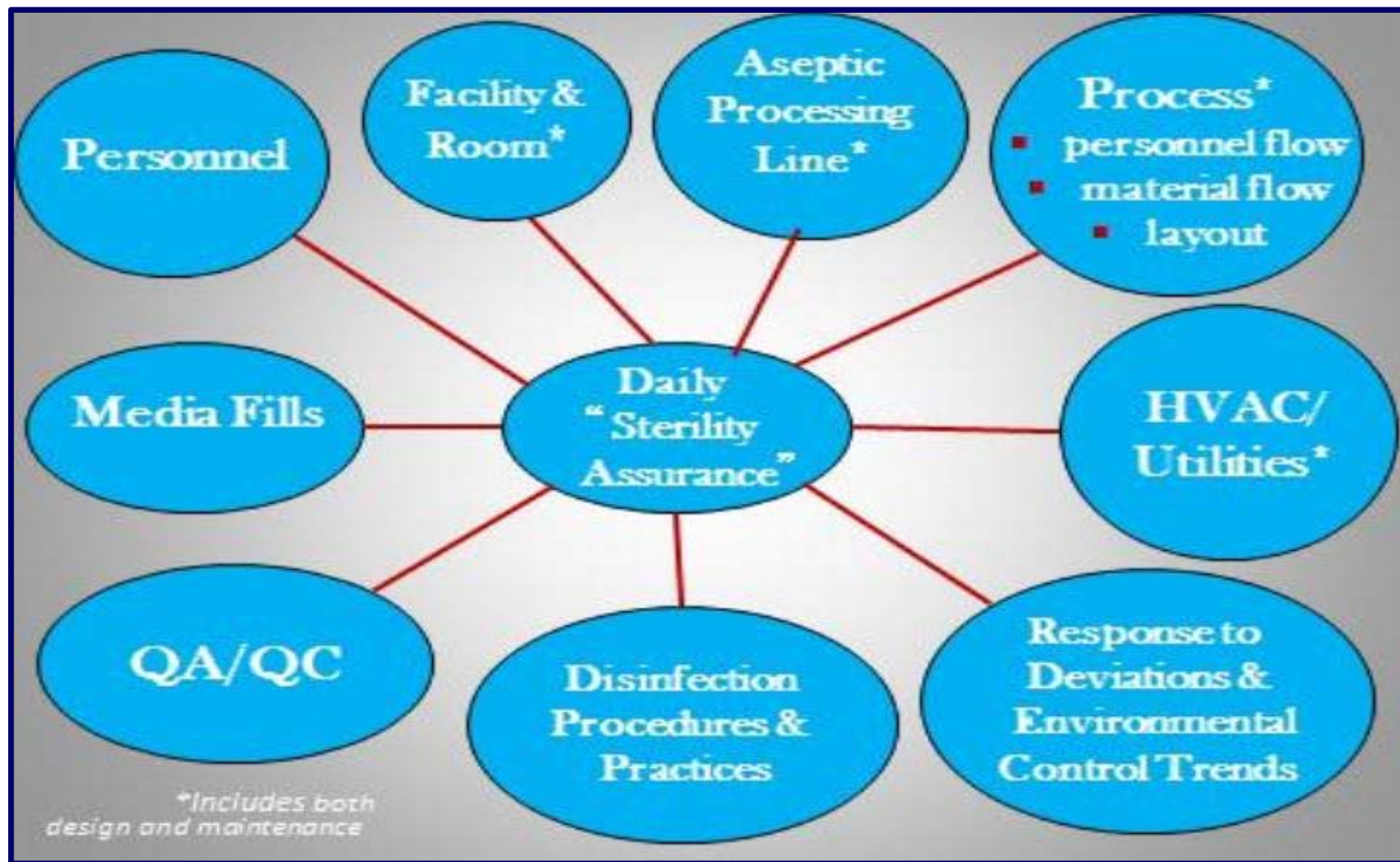
❖ Janet Woodcock, M.D., CDER Center Director (December, 2013)



Aseptic Processing: Many Variables

- Aseptic Processing requires daily vigilance and attention to many details
- A true test of CGMP conformance
- Adherence to procedures and details is fundamental to sterility assurance
- Process Consistency is of utmost importance for aseptic processing
 - Overriding objective is that *each unit produced in a batch is free of microorganisms*

Aseptic Processing: Many Variables



Aseptic Processing Complexity

The Holistic Facility

- Aseptic Processing requires “a strict **design** regime, not only on the process area, but on the **interactions with surrounding areas and the movement of people, materials and equipment** so as not to compromise the aseptic conditions.”

❖ *ISPE Sterile Manufacturing Facilities Guide*



Facility/Equipment Design

- It is essential for equipment to be designed to prevent entrainment of lower quality [surrounding] air into the critical area.

❖ *2004 Guidance on Sterile Drug Products Produced by Aseptic Processing*

Human Error – Is Retraining the Only Solution?

- Sciences of human factors engineering and human reliability analysis can provide valuable tools
- Human error may be more a symptom of an underlying problem rather than its cause.
- “...Errors can occur when a manufacturing process has not been sufficiently designed and validated... Also, problems may arise when work instructions, procedures, or policies are poorly written or designed,

- ... or when the operator-equipment or ***operator-process interface is poorly designed or difficult to use.***
- Therefore, it is useful to explore whether the existing manufacturing or other process may have contributed to the error or incident before assigning human error as the [primary] cause of the deviation or incident.”

❖ [O'Donnell, K. “Human Error and Retraining,” *IVT Journal*, 2009]

Human Factor Risks in Aseptic Manufacturing

Risk identification and mitigation is lifecycle responsibility...

Consider the *variability* in these critical Human-Machine interactions

- ✓ ***Routine*** Interventions
- ✓ ***Non-Routine*** Interventions: Fixing a Vial Jam or equipment malfunction
- ✓ ***Setup*** of equipment (Stopper Hopper, BFS Machinery, etc.)
- ✓ ***Disinfection*** of processing line and room
- ✓ ***Charging containers or closures*** onto a filling line
- ✓ ***Aseptic connections***
- ✓ ***Transfer of product*** (transfer of half-stopped vials to the lyophilizer; loading the lyophilizer, etc.)
- ✓ ***Aseptic addition*** of a non-filterable ingredient
- ✓ ***Wrapping parts and equipment*** for porous autoclave load
- ✓ ***Clearance of specified number (or all) units on the aseptic processing line*** because of major/extended intervention



Isolators are achieving the objectives of Advanced Aseptic Processing

2004 Aseptic Guidance provides incentive for isolators -

Appendix: Isolators “offer tangible advantages over traditional aseptic processing, including fewer opportunities for microbial contamination during processing.”

Isolators/barriers in Design section - Incentive also encourages:

- When possibility of contamination is higher (manually intensive lines), a larger number of units generally at or approaching full batch size is recommended. For **isolators**, a lower number of units as a proportion of overall operation may be used
- For *closed*, highly automated systems run on multiple shifts, a firm with a rigorous media fill design may be justified to conduct a lower number of total media fill runs. See FDA Q&A online.



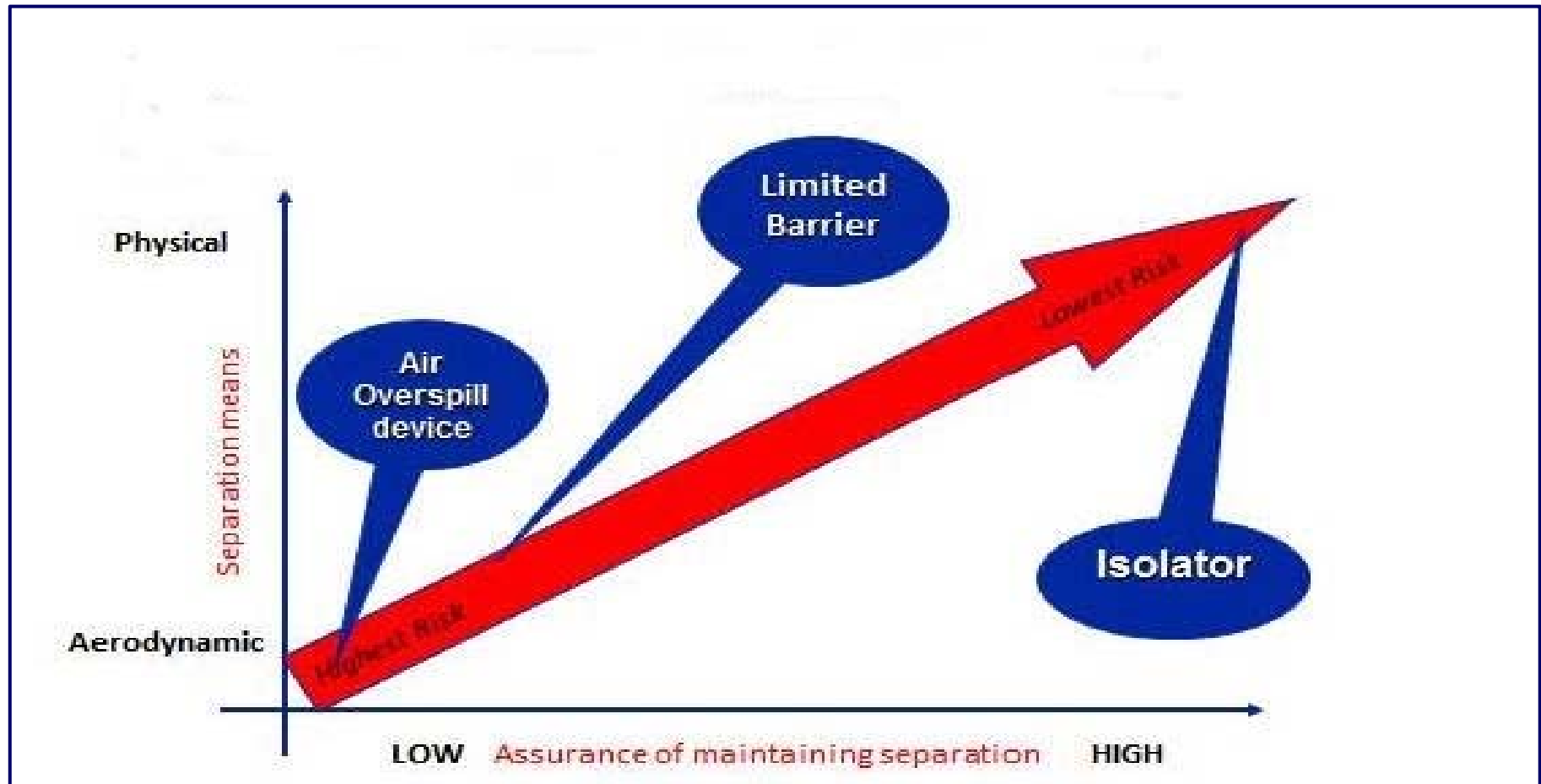
Restricted Access Barrier Systems (RABS)

“There are 2 types of RABS, ‘open’ and ‘closed’ RABS.

- The doors to a “closed” RABS are never opened during an operation.
- While an “open” RABS is designed to operate with doors closed at all times, on rare pre-defined circumstances the doors of the enclosure can be opened to perform certain interventions.
- If doors are routinely opened during a filling operation, the system is not considered a RABS because it no longer restricts access to the critical area. Typically, the cleanroom surrounding the RABS is controlled as a Class 10,000 (ISO 7) area and operators are fully gowned.”

❖ *Incentives for Closed RABS in FDA’s newly issued Compliance Program, 7356.002A*

Equipment Line Risk Reduction: Aseptic Processing (Open vs. Closed Systems)



[Adapted from Farquharson, G. "ISO 14644 - Part 7: Separative Devices,"
8th Pharmaceutical Isolator Conference Warwick, U.K. December, 2004.]



Automation

- “Design” section of Aseptic Processing Guidance...
 - SIP (Sterilize-in-Place)
 - Robotics
 - Other automated process steps to reduce risk
 - ✓ Automated transfers (e.g., lyophilizer loading)
 - ✓ Modern BFS (blow fill seal) operations
 - ✓ Rapid Transfer Port (RTP) or other transfer methods



Product Recall – Non sterility

Product - An anti-cancer drug indicated for patients with recurring metastatic carcinoma.

- **Microbial contamination** - Firm received multiple complaints from customers. Contamination initially appeared to be particles. It was further observed to be *“a large mass of free floating puffy particulate that looks as though fibers have been released and are also floating in the solution.”* Lab found the fungus **Penicillium species**. Source of contamination was apparently spores in the cleanroom, possibly further conveyed by personnel when performing aseptic addition of stoppers from stopper bag.
- Firm improved aseptic transfer and enhanced decontamination of the outer packaging of stopper bags. They also improved disinfection in other aspects of their operation and increased monitoring of critical equipment.

Contract Manufacturing Organization Risks - *Is the CMO capable and is oversight of operations acceptable?*

- “Not only are buyers unable to observe manufacturing quality, but firms that contract out manufacturing of their product ***often do not have the same level of insight into or oversight*** of the contract manufacturer’s quality systems as they would have into their own.
- ***Over-commitment on manufacturing capacity by a contract manufacturer can lead to*** an unsustainably high number of products on each line and ***substandard oversight of the process.***”

❖ [Woodcock, J and Wosinska M., Clinical Pharmacology & Therapeutics, “Economic and Technological Drivers of Generic Sterile Injectable Drug Shortage,” Jan 2013]



Managing Outsourced Activities

- Senior Management Responsibility extends beyond local site or corporation. Includes management review and control of...
 - *Outsourced activities (CMOs)*
 - *Quality of incoming materials (ingredient manufacturers)*
- **Prior to outsourcing operations or selecting material suppliers**, assess suitability and competence of the other party to -
 - *carry out the activity*
 - *provide the material using a defined supply chain*
- Examples of program elements -
 - *audits, material evaluations, quality agreement, monitoring and **reviewing supplier performance**, etc.*

❖ International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use - *ICH Q10*

Managing Risk Everyday Throughout the Lifecycle

- A drug manufacturer is responsible for implementing dependable daily operations that assure consistent drug quality.
- Management's daily decisions on myriad issues involving
 - equipment, materials,
 - maintenance, staff qualifications,
 - supervision, process control, and investigations

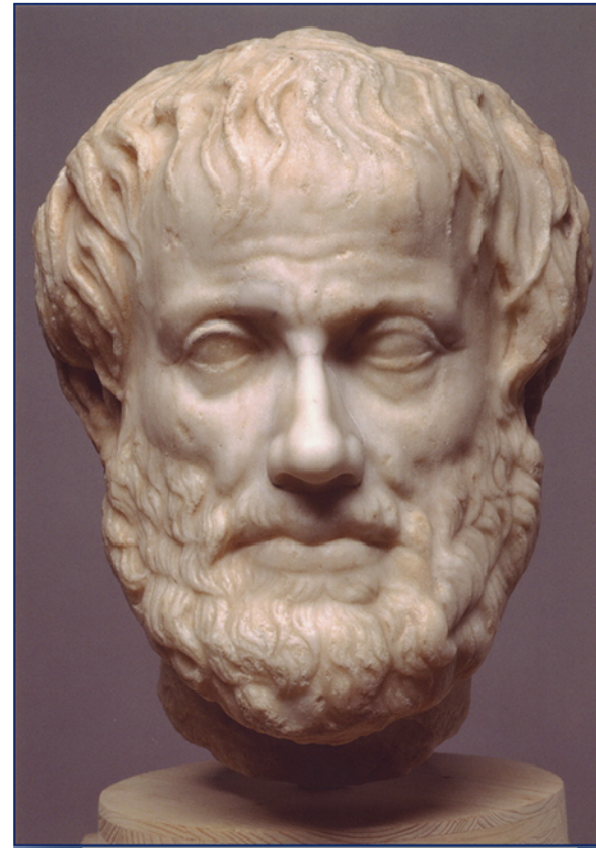
will **ultimately determine the quality** of the drugs that are shipped from a given facility.

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

A brief note

Regarding excellence –

“We are what we repeatedly do. Excellence, then, is not an act but a *habit*.”



Aristotle

All that said and so you know...



- April 1991 - A highly respected FDA Investigator mentioned, with regards to routine inspections, we (FDA) inspect about 5% of a manufacturing operations
- So then what is it that we (FDA) don't see that is below the water line, and
- Is the company aware of the other 95% that we (FDA) may never see



Finally a last note

“Integrity is doing the right thing even when no one is watching.”

❖ C.S. Lewis writes

Acknowledgement

**“How Mature Quality Systems Use QRM for Lifecycle Process
and Facility Improvement”**

Rick Friedman

*Deputy Director, Science and Regulatory Policy
Office of Manufacturing Quality / Office of Compliance
Center for Drug Evaluation and Research/FDA*

- ✓ PIC/S QPM Expert Circle Training Course – “Use of Advanced QRM by Regulatory Agencies” September 2016, London UK

DHANYAVAD !

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