Robust Aseptic Processing

PDA-Interphex
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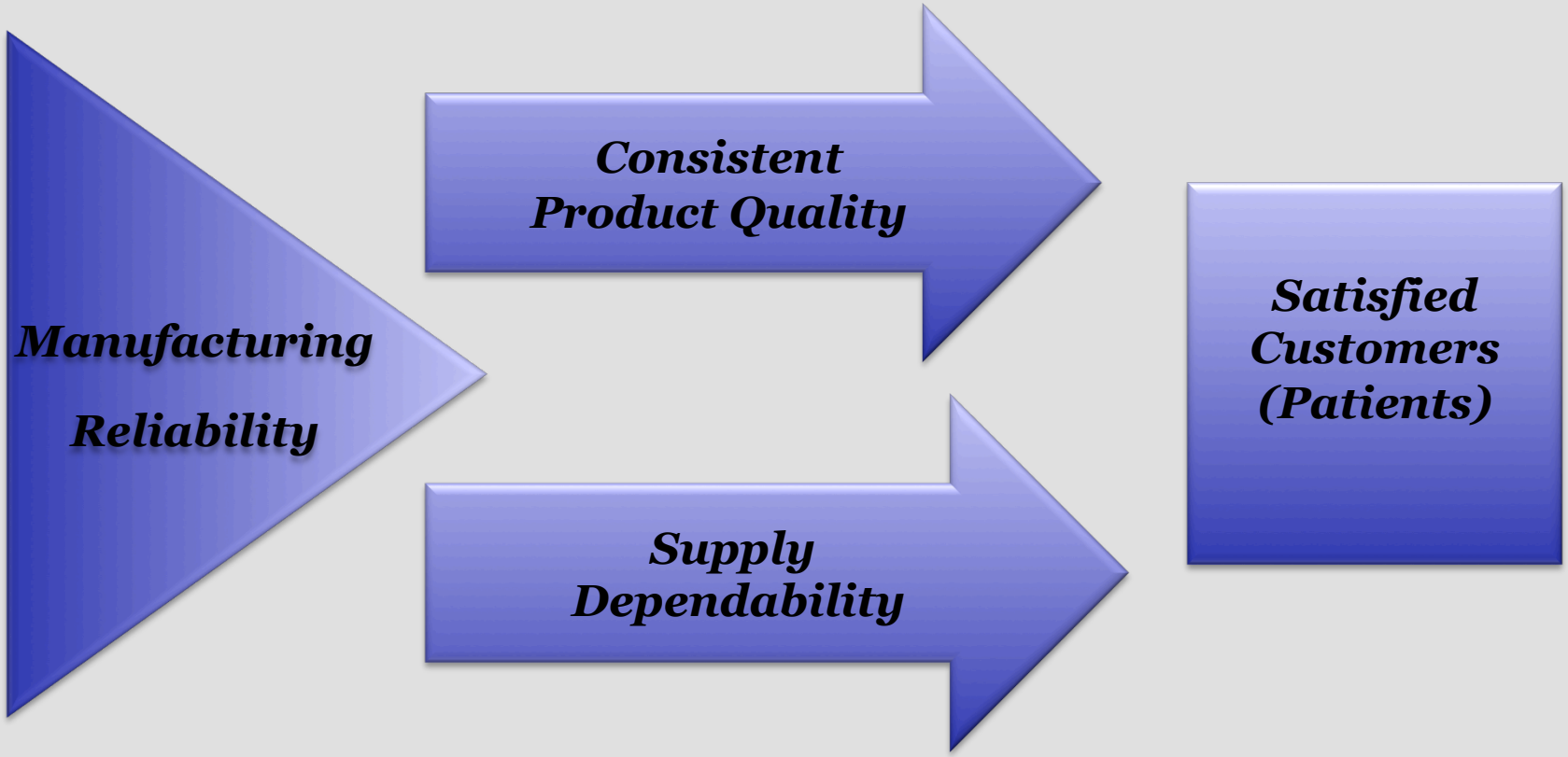
Richard L. Friedman, Associate Director,
Office of Manufacturing and Product Quality
Office of Compliance
Center for Drug Evaluation and Research
FDA

Topics

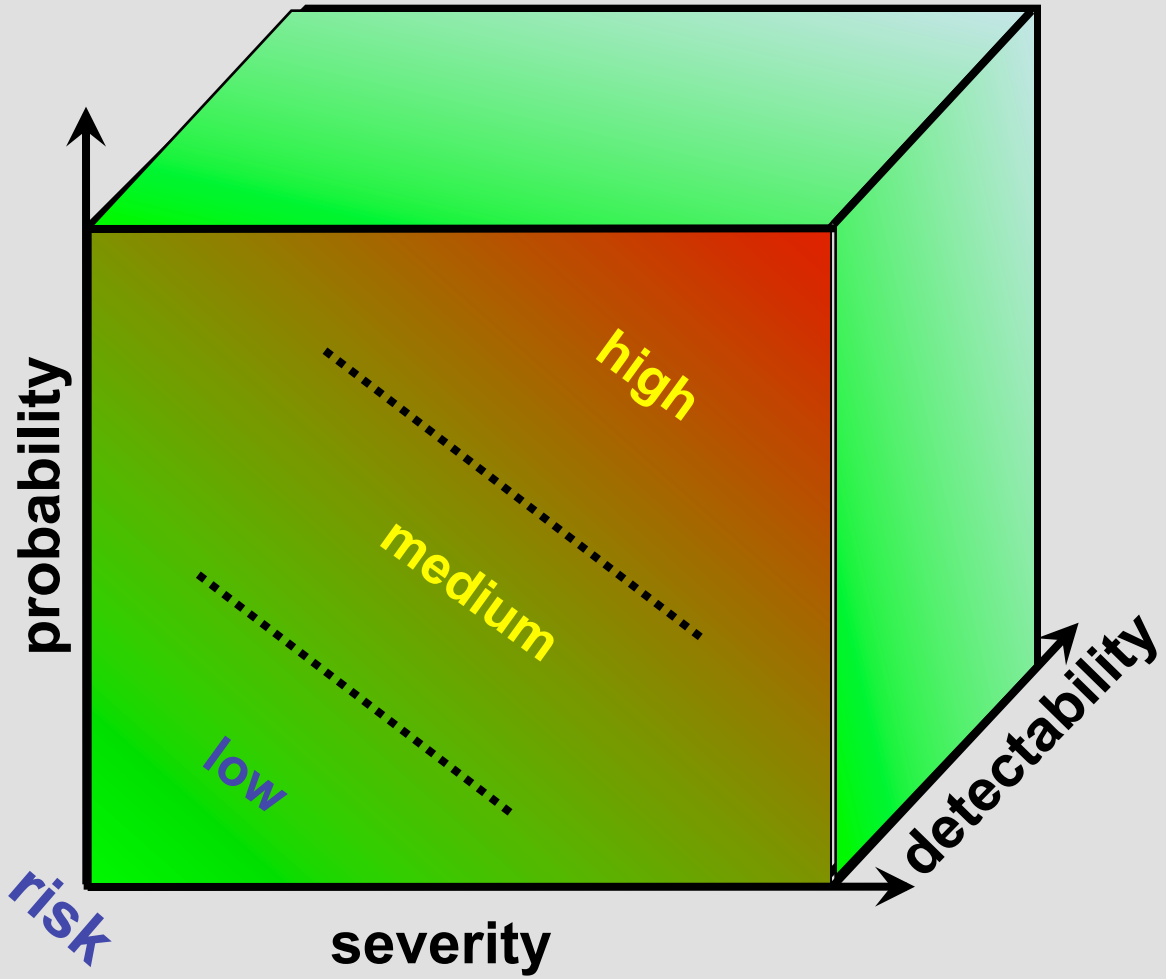
- **Lifecycle Quality Risk Management**
- **Sterile Drug Manufacturer Warning Letters**
  - Examples
- **Aseptic Processing Design**
  - Capability, Performance
  - Modernization

Lifecycle Quality Risk Management

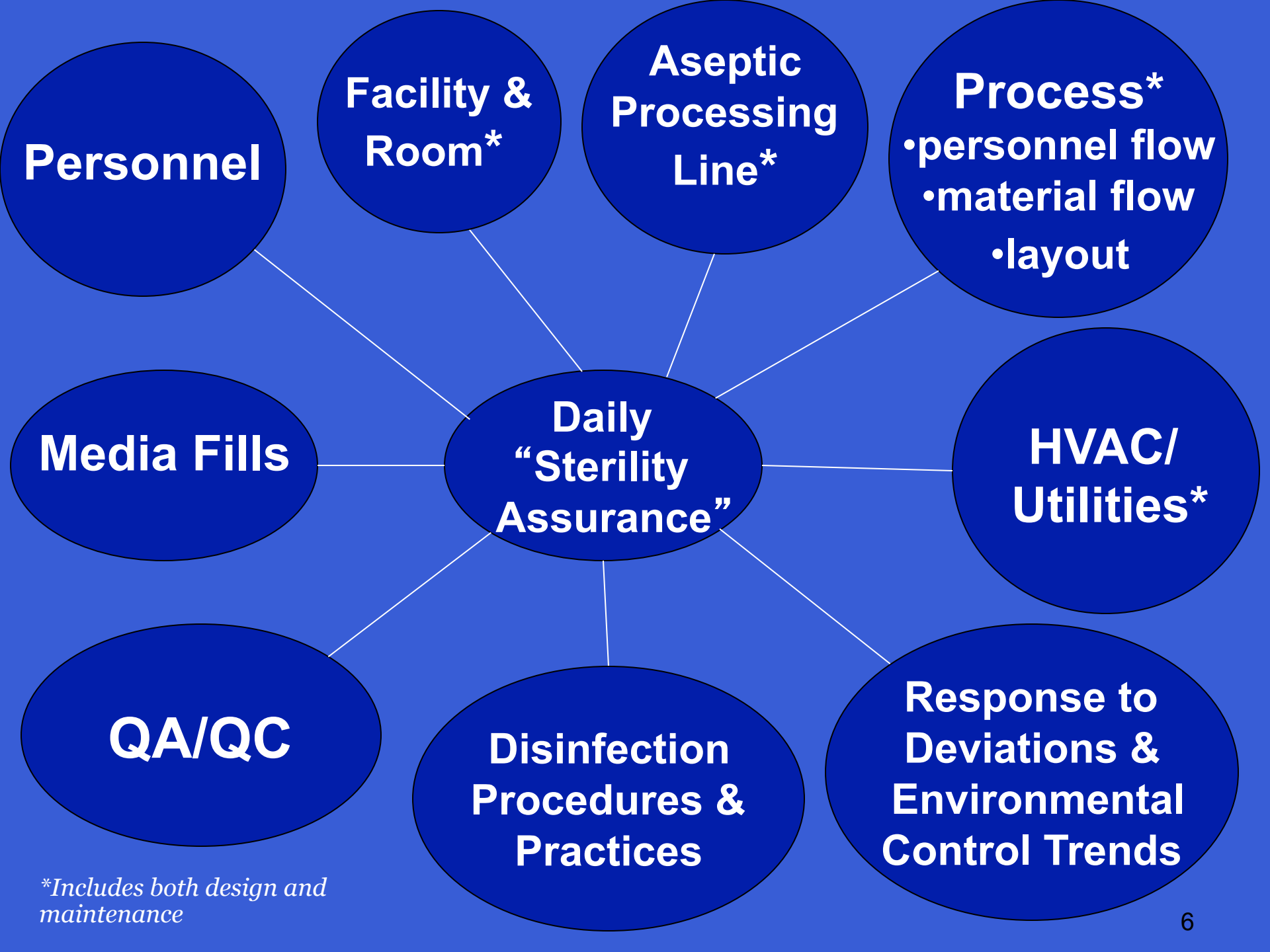

Manufacturing
Reliability
Consistent
Product Quality
Supply
Dependability
Satisfied
Customers
(Patients)

Risk-based approaches

Factors/ Parameters used to evaluate various risks



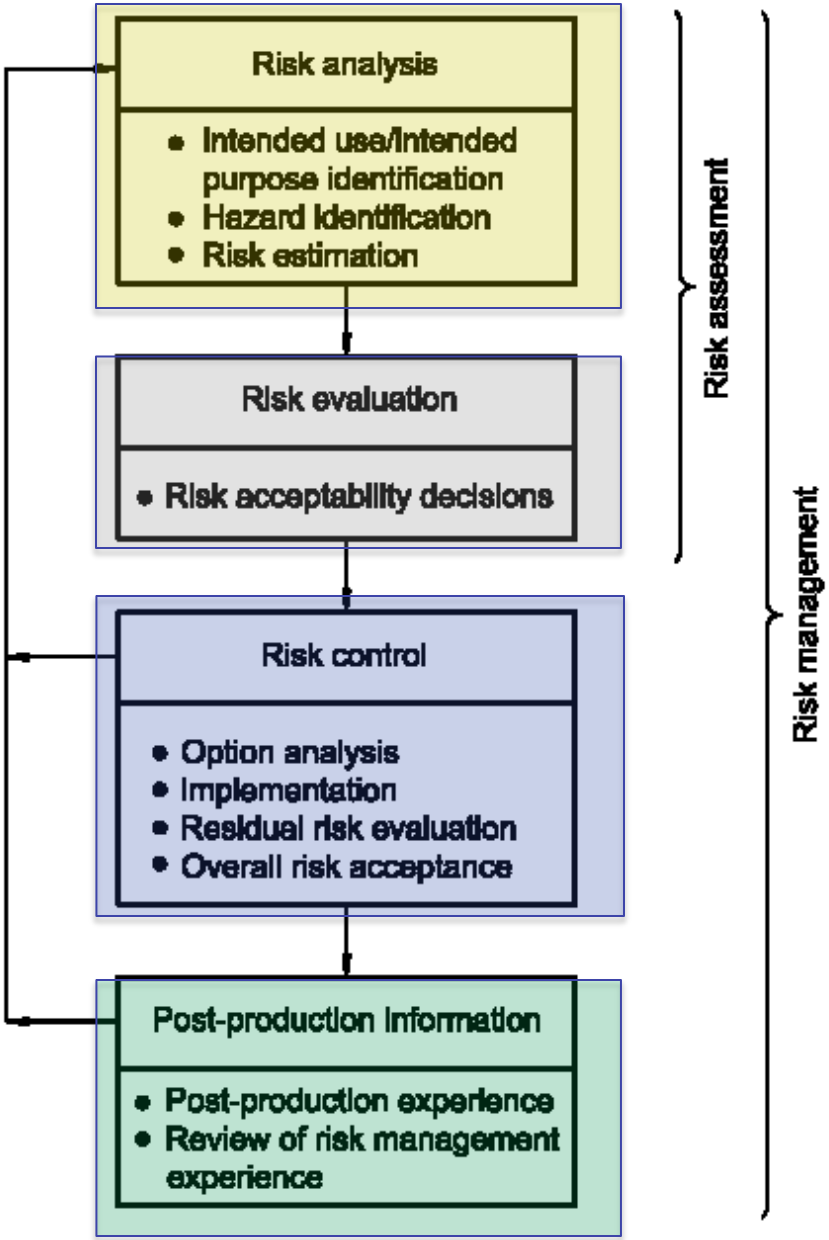
ICH Q9 EWG



*Includes both design and maintenance

[1]la·tent

- *adjective* \ˈlā-tᵊnt\ —used to describe something (such as a disease) that exists but is not active or cannot be seen


Risk analysis
• Intended use/Intended purpose identification
• Hazard identification
• Risk estimation
Risk evaluation
• Risk acceptability decisions
Risk control
• Option analysis
• Implementation
• Residual risk evaluation
• Overall risk acceptance
Post-production information
• Post-production experience
• Review of risk management experience
Risk assessment
Risk management

ISO 14971

Facility Design

Aseptic processing complexity requires a holistic design approach. Due to the interdependence of the various rooms that make up an aseptic processing facility, it is essential to carefully define and control the **dynamic interactions** permitted between cleanrooms.

Process Design

Aseptic processes are designed to minimize exposure of sterile articles to the potential contamination hazards of the manufacturing operation.

- limiting the duration of exposure of sterile product elements,
- providing the highest possible environmental control,
- optimizing process flow,
- limiting human interaction with the aseptic zone, and
- designing equipment to prevent entrainment of lower quality air into the Class 100 (ISO 5) clean area

People

Largest Risk to Sterility (we knew this in the 19th Century!)

- To touch with prepared hands the eyes, nose, mouth or clothing, and then touch a [sterile] dressing, would mean that infection would surely follow.
- Such a procedure would be an unpardonable violation of surgical cleanliness, a crime against asepsis.

[1897 Pharmacy Journal]

Examples of Sterile Drug Warning Letters

(note: paraphrased)

Warning Letter
Smoke Study Qualification

Smoke studies conducted by your firm in **four** filling rooms did not adequately demonstrate airflow directionality by performing personnel activities and interventions that are representative of the aseptic processes (as required by your SOP).

Warning Letter

Line Intended to Provide RABS Protection

- Non-integral and non-sterile gloves were used in aseptic processing of your injectable products. Visible holes and flaking were observed in the gloves worn by your operators. The gloves were used during aseptic processing of batch #-- and # ---, during the FDA inspection.

- Our investigators examined a sample of the remaining gloves from the same vendor lot in your warehouse. Similar defects were found in these gloves. In addition, we found that the primary glove packaging was broken or incomplete. QA released these gloves for use in production. In both intact glove packages examined for the integrity of the gloves inside, our investigators found the gloves to have visible holes, flaking, cracking, and/or discoloration. The cardboard boxes used to ship and store these gloves were also found to be damaged. Crushed insects were found on one glove's outer package inside the shipping box.

Warning Letter

Line Intended to Provide RABS Protection (cont'd)

- These defective gloves are especially concerning in part because they were used to perform manipulations directly over empty vials. During a brief 3-hour observation of your filling operation of --- Injection batch #--- in Suite ---, our investigators observed at least 20 line interventions using these gloves. We are also concerned that the RABS design positions the gloves over the sterile empty vials
- You also did not disinfect the conveyor after storage outside the ISO-5 area; this conveyor is used to transport filled and partially stoppered vials
- We also noted that your firm appears to frequently allow the RABS to be opened during processing. Please note that opening of the RABS during processing should be a rare event and used only for narrowly defined situations, not for routine interventions.

Warning Letter
Disinfection

Your firm's SOP lacks provisions to ensure adequate use of sporicidal agents. Sporicidal agents are not required on aseptic filling line stainless steel, non-removable components, and the ISO 5 rigid barriers… The SOP also lacks adequate details on how many times mops and wipes can be used. Your response is inadequate because you did not provide scientific data that the corrective actions are adequate. While this SOP instructs staff to replace mops, wipes, and other supplies when visually soiled, it is not clear that this revision provides for acceptable standards of sanitization and disinfection (for an ancillary area).

Warning Letter

State of Control (Terminal Sterilization Process)

- We are especially concerned that you have not identified the root cause that allowed the mold to proliferate to a level of TNTC (Too Numerous to Count) in several environmental samples directly over your filling line. Without identifying, correcting, and preventing the root cause of the mold growth at your sterile fill lines, the contamination hazard to the products manufactured on those lines could continue and potentially pose risk to patients.

- For your bioburden-based sterilization process, basic environmental control is integral to ensuring continuing sterilization process control by preventing an excessive challenge to the sterilization process.

- Firm was relying on parametric release program

Parametric Release Policy

- A firm may rely on a parametric release strategy and need not perform end-product sterility testing when the firm meets and documents assurances for both of the following conditions: First, the firm's **sterility assurance program must be in a state of control**. Second, for application products, the firm must have submitted all appropriate regulatory filings to FDA and be operating in conformance with its approved application.

Parametric Release - Parenteral Drug Products Terminally Sterilized by Moist Heat (FDA CPG) July, 2012

Warning Letter

LVP Bag Container-Closure Integrity

A bag leak was detected during routine microbiology testing. The investigation concluded that the root cause for the LVP bag leak was a weak membrane defect within the port component of the bag that resulted from machinery problems in the supplier's manufacturing process. The investigation identified 39 lots of finished drug product affected by the defect that were released for distribution. You also received consumer complaints identifying at least 10 membrane leaks and 155 inadequately-fitting blue caps over approximately 17 months. These are critical defects that can impact sterility… Describe your remediation plans to improve manufacturing robustness.

Modernization

Congressional Modernization Hearing

December 12, 2013

- "Inadequate manufacturing capability is a frequent cause of critical drug supply shortfalls."
- "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

Congressional Modernization Hearing

December, 12 2013

- Testimony cited need to "modernize manufacturing methods by taking advantage of advances in modern facility and process design, such as **replacing manually-intensive processes with automation, using closed systems, integrating process analytical technologies** into operations for better process control, and adopting continuous manufacturing platforms. These technologies would help achieve improved manufacturing reliability, increased robustness, and lowered costs."

Janet Woodcock, M.D., CDER Center Director

Contemporary Design Approaches

- Separation
  - e.g., isolators, closed RABS
- Automation
- Integration
  - Minimize or "design out" risks of transfers between unit ops
- Advanced Testing/Analytics
  - Improved testing, trending techniques

Automation/Integration

Principles:

- **Any intervention or stoppage** during an aseptic process can increase the risk of contamination.
- **The design of equipment** used in aseptic processing should limit the number and complexity of aseptic interventions by personnel.

Examples of Risk Mitigations:

- Automation of process steps, including the use of technologies such as robotics, can reduce risk to the product.
- Automated Transfers
  - direct product flow, often from a lower to a higher classified area
  - including lyophilizer loading, dry heat oven, RTP, double-door or integrated sterilizer

– SIP/CIP instead of making aseptic connections

Isolators

Isolators "offer tangible advantages over traditional aseptic processing, including fewer opportunities for microbial contamination during processing."

2004 FDA Aseptic Guidance

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, in 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 areas. 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 are found in FDA's newly issued Compliance Program, 7356.002a

Congressional Modernization Hearing

December, 12 2013

While this may require some investment for manufacturers who need to improve the infrastructure, the benefits of more dependable operations strongly aligns with the business goals of process predictability (e.g., Right First Time) and product dependability. Reduced variability will lead to reduced rejected goods, higher supply dependability, fewer defects, and overall better productivity and profitability. Modernizing drug manufacturing represents a great opportunity to lower costs and develop more flexible manufacturing processes… The public health will also be well served as modernization can help reduce the root causes of drug shortages.

Janet Woodcock, M.D., CDER Center Director

FDA References

- Sterile Drug Products Produced by Aseptic Processing
  http://www.fda.gov/downloads/Drugs/.../Guidances/ucm070342.pdf

- Sterile Process Inspections (FDA inspection program manual)
  http://www.fda.gov/downloads/ICECI/ComplianceManuals/CompliancePrograMManual/UCM125409.pdf

- Compliance Policy Guide – Parametric Release (Moist Heat)
  http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm312974.htm

- Guidance on Submitting Sterilization Documentation…
  http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072171.pdf