

Aging Facilities: An FDA Perspective

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Objectives

- **FDA's Perspective on Aging Facilities**
- **Potential Impact of Aging Facilities**
- **Modernization**
- **GMP Inspectional Approaches**

What are Aging Facilities?



Not **Designed** or **Intended** to be a hybrid...

What are Aging Facilities?

- Do your systems currently have the capability to meet the demands of your operational goals?
- Are your systems/equipment in need of improvement?
- Are your manufacturing facilities, processes, and testing facilities becoming obsolete?
- Does the facility have sufficient capacity for the current output?

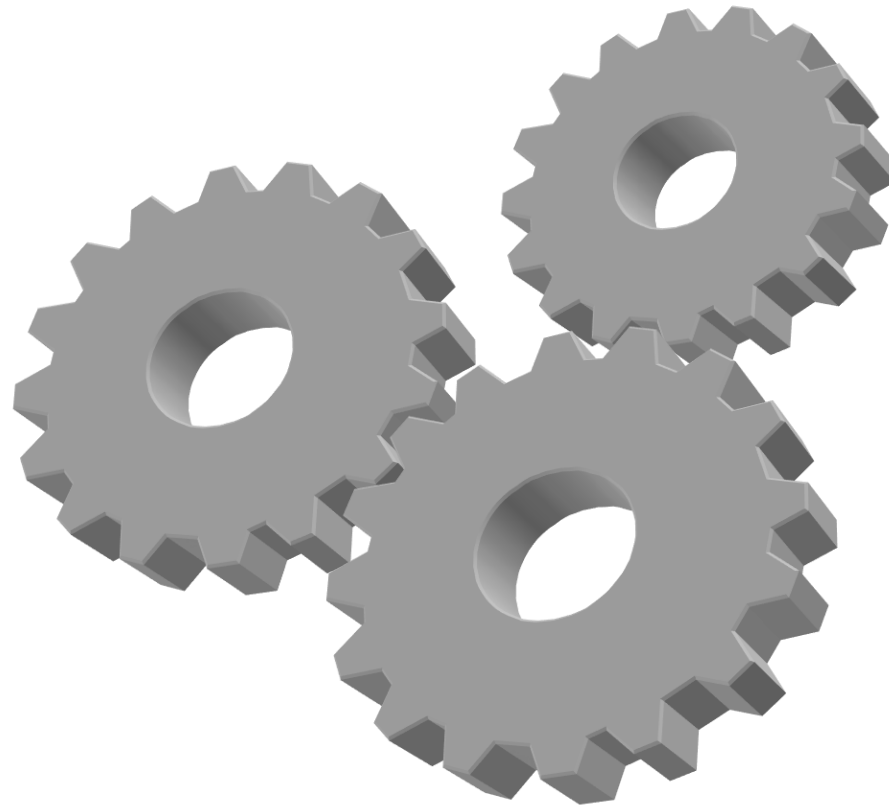
Is your facility designed for how you currently intend it to be used?



What are Aging Facilities?

- Manufacturing facilities with multiple challenges...For examples:
 - Less efficient operations
 - Material flow
 - Personnel flow
 - Broken down HVAC systems
 - HVAC systems requiring upgrades
 - Old equipment that cannot keep up with manufacturing demands

FDA's Perspective on Aging Facilities



FDA's Perspective

- Are there high risks or the potential for high risks of not meeting cGMPs?
 - Per FDA, the “c” in GMP stands for **“current”**. This means that companies should be using technologies and systems that are “up to date” in order to comply with the regulations.
- Are your systems and equipment adequate enough to prevent contamination, to eliminate potential mix-ups?
- Do you experience errors that maybe were okay 10 or 15 years ago, but would not be acceptable under today's standards?
- Are you experiencing an uptick in errors?

FDA's Perspective

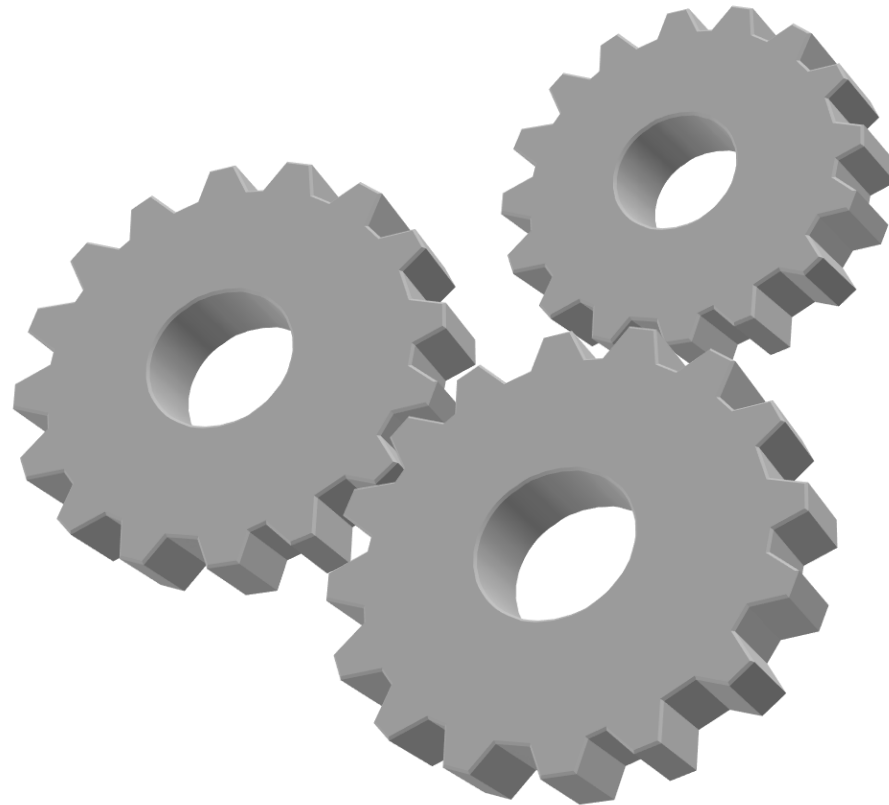
- FDA assesses the facility and processes as they relate to cGMP and the CFR

Q: Does an older facility **ALWAYS** mean an aging facility?

A: **Not necessarily...**

- What programs does your firm have in place to ensure that the facility and processes continue to operate properly? (e.g., Change Control, CAPA)

Potential Impact of Aging Facilities



What has the FDA found?

- “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.”
- Inadequate manufacturing capability is a frequent cause of drug defects and critical drug supply shortfalls

Janet Woodcock, M.D., CDER Director

Challenges to Pharmaceutical Quality

*“ There have been alarming shortages of critical drugs over the past few years. Many of these shortages were caused by the use of outdated equipment, reliance on **aging facilities** operating at maximum production capacity, and lack of effective quality management systems.”*

FDA Office of Pharmaceutical Quality White Paper, 2015

Congressional Hearing on Drug Shortages

February 10, 2014

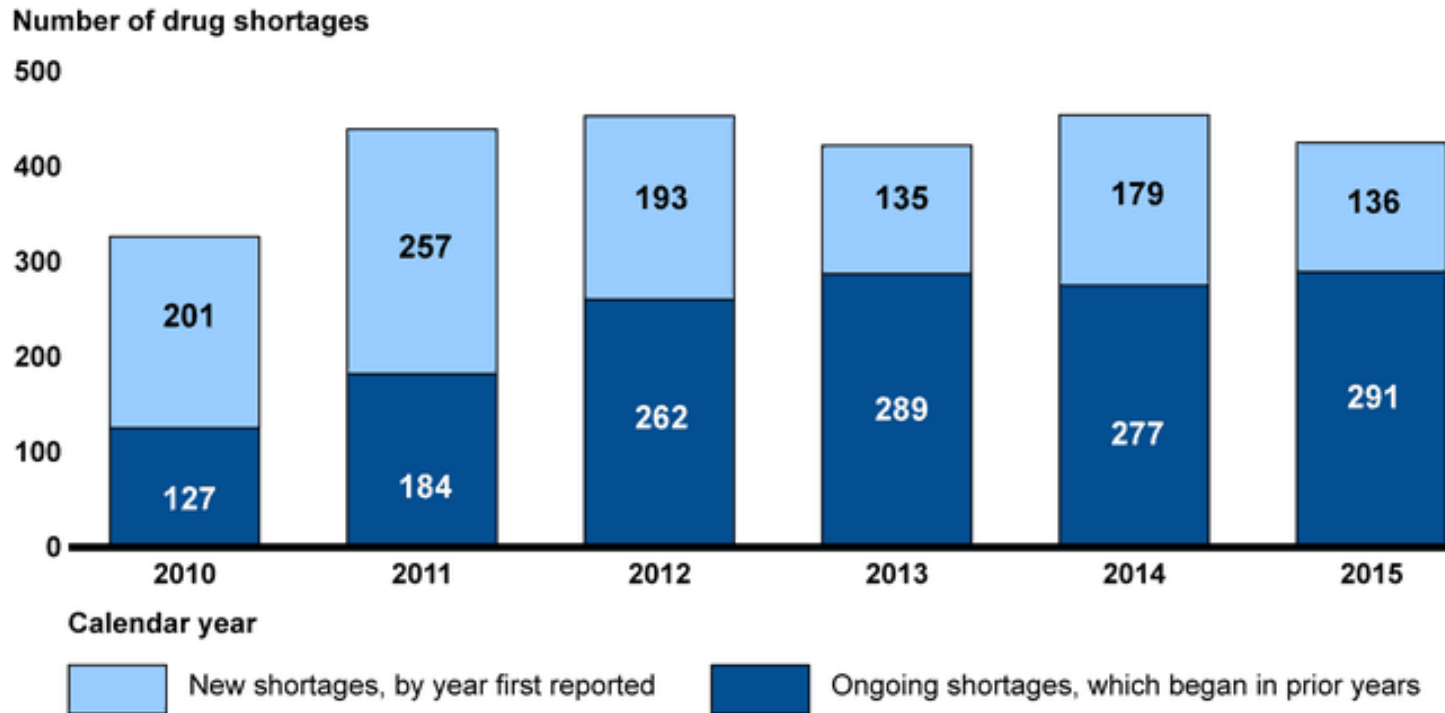
*“Most often, however, production disruptions leading to shortages are the result of failures within manufacturing facilities that result in failures of product or facility quality... Moreover, just like an older car, **aging** production lines and the facilities that house them require significantly more upkeep...Addressing these quality problems can result in a supply disruption that can result in a drug shortage.”*

Dr. Douglas Throckmorton, FDA Deputy Director for Regulatory Programs

What has GAO Found?

“When available supplies of prescription drugs are insufficient, patient care may be adversely affected.”

Number of Drug Shortages from January 2010 through December 2015



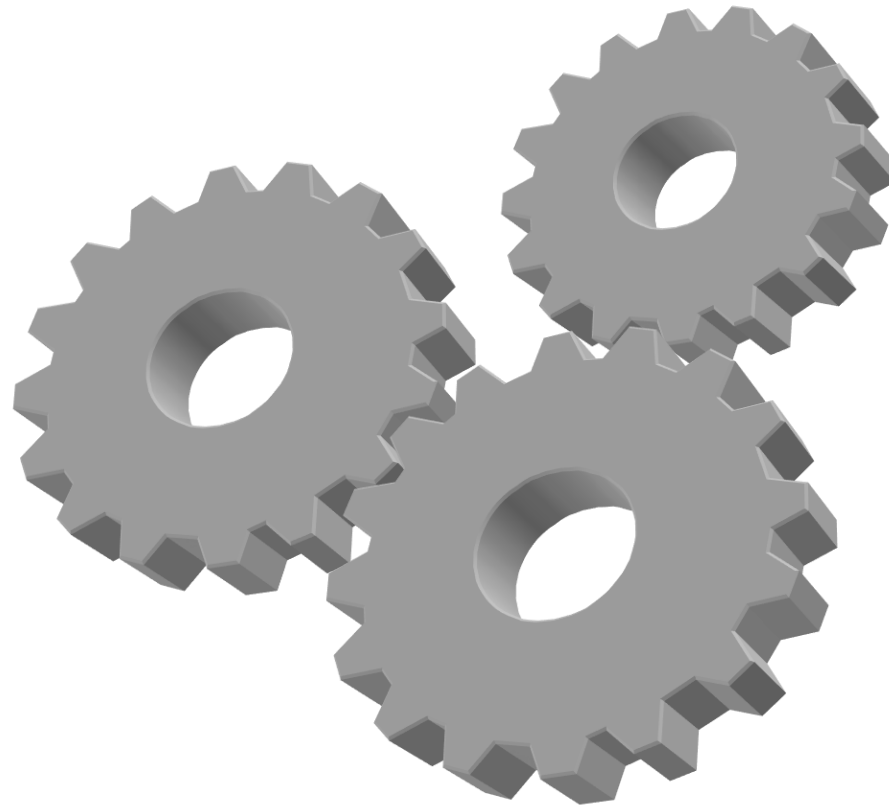
Source: GAO analysis of University of Utah Drug Information Service data. | GAO-16-595

CDER Drug Shortage Office

- CDER Drug Shortage Staff tracks reasons for shortages and **Quality** remains the #1 reason
- **Aging** Facilities and/or Outdated Equipment can be the cause
- Shortage risks can be decreased through **upgrades**, redundancy in manufacturing operations

<https://www.accessdata.fda.gov/scripts/drugshortages/default.cfm>

Modernization



Aging Facilities-How Do We Stay Current?

- Is your facility keeping pace with today's standards for technology and regulatory expectations?
- Does your facility have sufficient capacity for the current output?
- Have you looked at your facility? Are there ways you could better maintain or upgrade your 10, 20, 30, 40...year old facility?
- Have you conducted a quality risk assessment? Do you have appropriate controls in place to ensure there are no potential risks to product quality and ultimately, to patient safety?
- Is it time to rebuild or install new technology / new equipment to protect products, meet current regulations, and to keep up with today's demands? (e.g. RABS, isolators...)



Congressional Hearing on Modernization December 12, 2013

“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 Director



Congressional Hearing on Modernization *cont'd* 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 Director

Paradigm Shift

Manual Interactions

vs.

**Modernization to
Remove Human to
Machine Interactions**



Contemporary Design Approaches

- Separation
 - e.g., isolators, closed RABS, Blow-Fill-Seal
- Automation
- Integration
 - Minimize or “design out” risks of transfers between unit operations
- Advanced Testing/Analytics

2004 FDA Aseptic Guidance

- **Isolator Technology** “offer tangible advantages over traditional aseptic processing, including **fewer opportunities for microbial contamination** during processing.”
- **Blow-Fill-Seal Technology** “includes economies in container closure processing and **reduced human intervention** and is often used for filling and packaging ophthalmics, respiratory care products, and less frequently injectables.”

The Case for Automation/Integration-

Ensuring you are maintaining the “current” in cGMP

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:

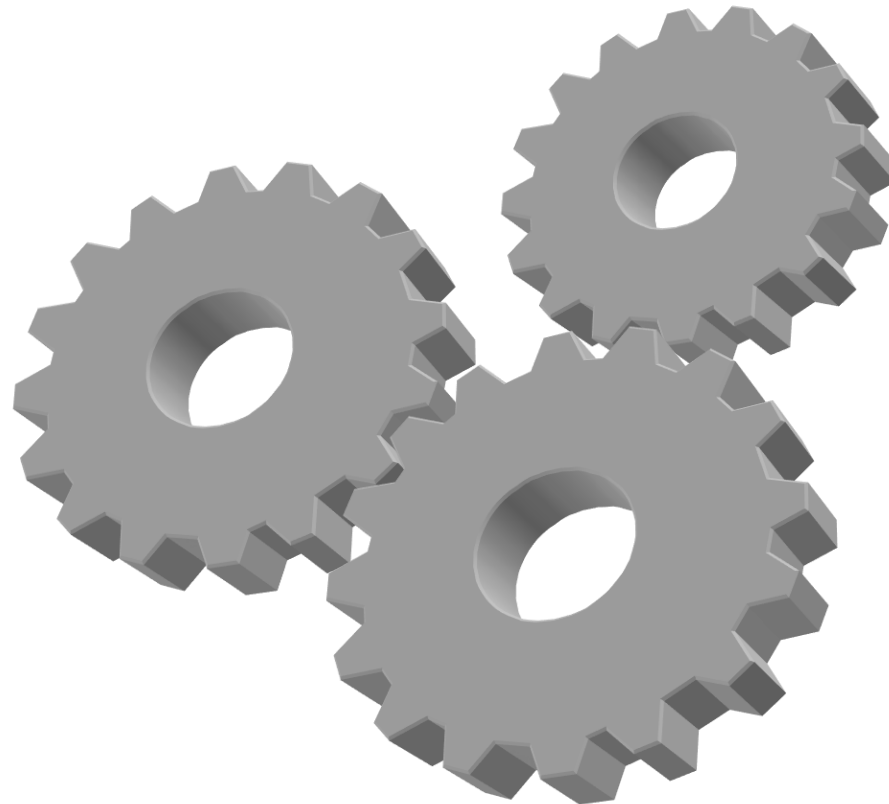
- Automation of process steps, including the use of technologies such as robotics, can reduce risk to the product.
- Automated Transfers
 - direct product flow, often from a lower to a higher classified area
 - including lyophilizer loading, dry heat oven, RTP, double-door or integrated sterilizer
-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

Modernization Challenges

- Modernization may be costly
- Time-consuming e.g., may require shutdowns
- Changes may require regulatory approval



GMP Inspectional Approaches



GMP Inspection

C.P. 7356.002-Systems-based approach inspection (Quality, Facilities & Equipment, Materials, Production, Packaging & Labeling, and Laboratory Systems):

Quality System:

- No Quality Control Unit
- Failure to review/approve procedures.
- Failure to document execution of operations as required.
- Failure to review documentation.
- Failure to conduct investigations and resolve discrepancies/failures/deviations/complaints.
- Failure to assess other systems to assure compliance with GMP and SOPs.

GMP Inspection *cont'd*

Production System:

- Failure to establish/follow a control system for implementing changes in production system operations.
- **Adequacy of equipment and facility for intended use**
- Failure to document investigation of discrepancies.
- Lack of process validation.
- Lack of validated computerized processes.
- Incomplete or missing batch production records.
- Nonconformance to established in-process controls, tests, and/or specifications.
- Lack of validation of water systems depending on the intended use.

GMP Inspections of Aging Facilities

- Annual Product Reviews
- Field Alert Reports (FARs)
- Recalls
- Complaints
- Change Controls
- Deviations
- Equipment in Disrepair
- Maintenance and Preventive Maintenance records
- CAPAs
- Cleaning records
- Media Fills
- Equipment usage logs
- Multiple sets of data
- Employee practices in Aseptic areas
- Rejected/reworked batches
- Observed vs Validated practices

FDA Efforts

- **Office of Pharmaceutical Quality**
 - “One Quality Voice”
 - Enhancing quality oversight throughout drug lifecycle
- **Emerging Technology Program**
 - Modernizing Pharmaceutical Manufacturing
 - Innovative approaches to product design and manufacturing

The Path Forward...

- We are encouraging those with aging facilities to upgrade/modernize to stay **“current”**
- FDA’s oversight is related to a firm’s ability to manage risk associated with product quality
- Mutual goal to reduce and prevent drug quality and shortage issues

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Questions

