Aging Facilities toNew Technologies:

The Regulatory Impact on GMP Manufacturing Facilities and Product Licensed Applications.

Linda Kramer

Terry Ward

Aging Facilities toNew Technologies

- The presentation will cover the complications associated with keeping an aging Biological manufacturing facilities to remain cGMP compliant.
- The implementation of novel technologies such as single use bags/connectors, inprocess analyzers, and isolator technologies in both aging and new pharmaceutical manufacturing facilities.
- Impact ofsuch regulatory compliance hot topics i.e. Validation/Qualifications andData Integrity on Biological Licensed Product Applicationsand Regulatory Inspections.

Presentation Outline

- Open Question Discussion
- Aging Facility Concerns
- To Build New Facility or Not
- Implementation of novel technologies such as single use bags/connectors, inprocess analyzers, and isolator technologies in both aging and new pharmaceutical manufacturing facilities
- Data Integrity Issues
- Hot topics from FDA

QUESTION

Open discussion

Aging Facility Concerns

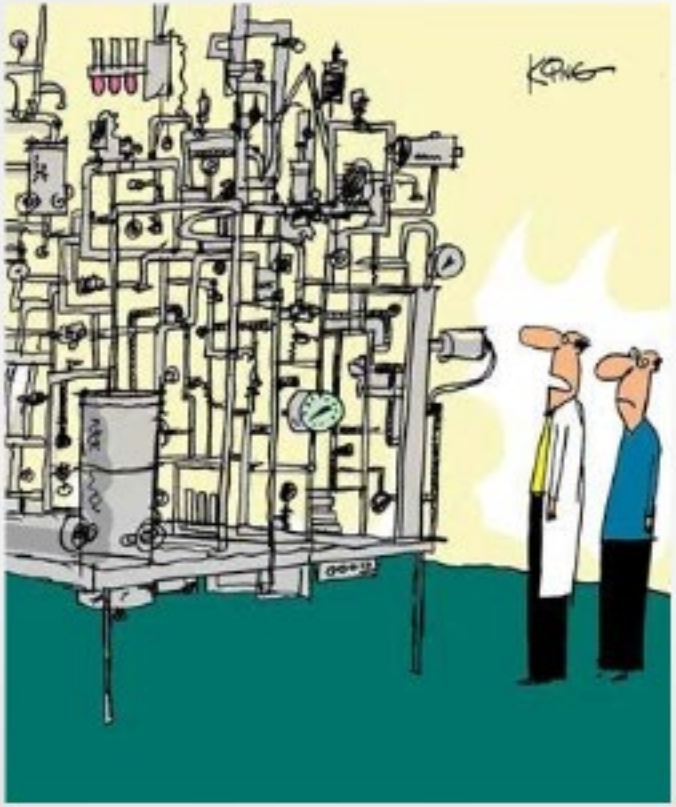
Concerns with AgingFacilities

- Compliance issues
- Contamination issues
- Inspectional Issues
- Possible product shortages onthe market
- Modernization needed
  - Recapitalization
  - Time
  - Hold of product
  - Process validations

Regulations with Impact on Aging Facilities

- "c" in GMP
- QA and Regulatory compliance is your first source
- 21 CFRS!!200s, 600s, 800's
- Q9 – Riskmanagement of facilities, equipment andutilitiesand preventive maintenance
- Q10 - A management review system shouldidentify appropriate actions such as improvements to manufacturingprocessesand products
- Guidance to Industry, ProcessValidation: GeneralPrinciples and Practices
  - Maintain process ina state of control over the life cycle of the process, evenas materials, equipment, production environment, personnel, and manufacturing procedures change
  - Guidance supports process improvement and innovation through sound science
- Advancement of Emerging Technology Applications for Pharmaceutical Innovation and Modernization Guidance for Industry
- https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM478821.pdf

To Build New Facility or Not? That is the Question



"Fortunately I willbe retired before it is validated"

Compliance and Regulatory Impact on Aging ManufacturingFacility

- The firm must decide to make improvements or not to the aging Facility?
  - Modernization – extension useof Facility?
  - Discussion on product and process impact
  - New Building, improvements toAging Facility, useCMO
  - New Technologies – Disposables, Modularunits
- Discussions with FDA on pathways for Regulatory options formodernization with minimal impact?
  - Go to theFDA with a plan that is well thought out and includes defined expectations for the meeting/discussion
  - Type C meetings
  - Comparability protocols

Facility Design Newvs Retro fit

- New Facility
  - Easy to incorporaterequirements
  - New Equipment, flows
  - Modern state of artequipmentcan be installed
- Retro fitfacility
  - Regulations must befollowed to breakdown and bring up facility afterchanges
  - Difficulty for construction materials depending on age of facility
  - Flows, space, equipment
  - Considerations of containment, contamination (mold)

Facility Design Sustainability

- Quality by Design
- Continuous Manufacturing
  - https://www.fda.gov/Drugs/NewsEvents/ucm557448.htm
  - Bio Task force and FDA is looking for industry tolead in this area
- New or Retro Fit facility consider sustainabilityfor future
  - https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatory Information/Guidances/UCM478821.pdf
  - Build in flexibility in design
    - Processing – multiple products
    - Equipment– state of art equipment
  - Environmental considerations – Utilities and use

Implementation of novel technologies such as single use bags/connectors, in process analyzers, and isolator technologies in both aging and new pharmaceutical manufacturing facilities

Recent FDA News-Advanced Manufacturing Technology

- FDA says it has awarded five grants to higher education institutions and non-profit organizations to study and recommend improvements for the continuous manufacturing of biological products, aswell as similar innovative monitoringand control techniques.
- FDA commissioner Scott Gottlieb says advanced manufacturing technologies "hold great promise for improvementsin the reliability, flexibility, and cost-effectiveness of manufacturing for biological products.These platforms maybe crucial to unlocking the full potentialof very novel technologies like cell and gene therapies, and new vaccines. Grants like these help encourage the establishment of high techmanufacturing platforms in the U.S., potentially providing an opportunity to bring more manufacturing back to Americansoil."
- FDA has developed CBER and CDER group called INTERACT to discuss novel technologies.

Facility Life expansion by implementing single use disposable technology such as bags/connectors/isolators

- Challenges to address for FDAapproval
  - Leachable/Extractable
  - Containerclosure study
  - Leaking
  - Particulates
  - Appropriate Risk Assessment
  - EducatingFDA reviewers

Facility Life expansion by implementing single use disposable technology such as bags/connectors/isolators

- Industry advantages
  - Less cleaning validations required
  - Less cross-contamination issues
  - Smaller design space areas depending ontechnology used
  - Modular manufacturing skids allowing for mobile units and smaller scale that can be used for cellgene therapy manufacturing
- Disadvantages
  - Cost

Data Integrity Issues and Hot Topics inFDA

Data Integrity Issues

- Current environment– Risk for Data Integrity Issues
- Examples of Recent Warning Letters referencing aging facilities
- Data Integrity Issues
  - In aging Facility and new Facility
  - 21 CFR Part 11 compliance
  - Audit trails
  - SAP

Current environment– risk for data integrity issues

- –Overseastesting and manufacturing
- –Supply chain
- –Outsourcing of operations (e.g., QC labs, manufacturing)
- –Economicstressors– cuttingcorners
- –Data review practices
- –Increasing use of electronicsystems without commensurate understanding and implementation of risk-based control for electronic data integrity
- –Controlsto **prevent data integrity issues**
- –Controlsto **detect data integrity issues**

Examples of Recent Warning Letters referencing aging facilities

Adobe Acrobat Document

Adobe Acrobat Document

Current environment– risk for data integrity issues

- MHRA issued "GMP Data Integrity Definitions and Guidance for Industry" whichhas established an expectation that pharmaceutical manufacturers,importersand contract laboratories, as part of their self-inspection programme, must review the effectiveness of their governance systems to ensure data integrity and traceability.
  - https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/412735/Data_integrity_definitions_and_guidance_v2.pdf

- **FDA Data Integrity and Compliance With CGMP Guidance for Industry**
  - https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM495891.pdf

Data Integrity Issues in Aging Facilities and New Facilities

- 21 CFR Part 11 compliance
- Audit trails
- SAP

Hot topics in FDA

- QbD – building design space into process early onin process
  - There have been some successes in CDER
  - Gives industry freedom to operate
- Discussion on regulatory scrutiny over changes
  - Hasn't yet been adopted by FDA
- Consistent review of submissions and inspections – new PDUFA to be catalyst for FDA
- Quality Metrics
  - Develop metrics forrisk assessment
  - Less review and inspections
  - Look at overall state of facility
  - Ensure Quality and become patient centric


THANK YOU

ReferenceFDA Regulations

21 CFR

Title 21 Code of Federal Regulations (CFR)

• Part 11	eRecords,& sig
• Parts 25,50, 54, 56, 58	EI; humans; FD, IRBs; GLPs
• Parts 201, 202	Labeling & Advertising
• Parts 210& 211	GMPs
• Part 312	IND
• Part 314	Application for newdrug approval
• Part 316	Orphan Drugs
• Parts 600- 680	Biologics& Licensing

Guidance documents

- There areseveral Industry guidance documents that FDA uses. Check FDA website:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ UCM079645.pdf

- Some Facility related guidance's
  - Changes to an approved NDA orANDA
  - Sterile Drug Products produced by aseptic processing
  - Guidance for Industry: Changes To An approved Application: Biological Products

Facility Design Regulations

- 21 CFR 211 part C Buildings and facilities
  - 21 CFR 211.42 Design and construction features
    - Any building or buildings used in the manufacture, processing, packing, or holding of a drug productshall be of suitable size, construction and location to facilitate cleaning, maintenance, and proper operations.
    - Includingadequate areas for equipment,area for processing to prevent mix ups…
  - 21 CFR 211.46 Ventilation, air filtration, air heating and cooling.
  - Lighting , plumbing, sewage, washing facilities, sanitization, maintenance