Aging Facilities to New Technologies:

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Aging Facilities to New 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 of such regulatory compliance hot topics i.e. Validation/Qualifications and Data Integrity on Biological Licensed Product Applications and 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 Aging Facilities

- Compliance issues
- Contamination issues
- Inspectional Issues
- Possible product shortages on the 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 – Risk management of facilities, equipment and utilities and preventive maintenance
- Q10 - A management review system should identify appropriate actions such as improvements to manufacturing processes and products
- Guidance to Industry, Process Validation: General Principles and Practices
  - Maintain processes in a state of control over the life cycle of the process, even as 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

ISPE LK and TW 10/09/2018
To Build New Facility or Not? That is the Question
“Fortunately I will be retired before it is validated”
Compliance and Regulatory Impact on Aging Manufacturing Facility

- The firm must decide to make improvements or not to the aging Facility?
  - Modernization – extension use of Facility?
  - Discussion on product and process impact
  - New Building, improvements to Aging Facility, use CMO
  - New Technologies – Disposables, Modular units
- Discussions with FDA on pathways for Regulatory options for modernization with minimal impact?
  - Go to the FDA with a plan that is well thought out and includes defined expectations for the meeting/discussion
  - Type C meetings
  - Comparability protocols
Facility Design New vs Retro fit

- New Facility
  - Easy to incorporate requirements
  - New Equipment, flows
  - Modern state of artequipment can be installed
- Retro fit facility
  - Regulations must be followed to breakdown and bring up facility after changes
  - 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 to lead in this area
- New or Retro Fit facility consider sustainability for future
- 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, as well as similar innovative monitoring and control techniques.
- FDA commissioner Scott Gottlieb says advanced manufacturing technologies “hold great promise for improvements in the reliability, flexibility, and cost-effectiveness of manufacturing for biological products. These platforms may be crucial to unlocking the full potential of very novel technologies like cell and gene therapies, and new vaccines. Grants like these help encourage the establishment of high tech manufacturing platforms in the U.S., potentially providing an opportunity to bring more manufacturing back to American soil.”
- 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 FDA approval
  - Leachable/Extractable
  - Container/closure study
  - Leaking
  - Particulates
  - Appropriate Risk Assessment
  - Educating FDA 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 on technology used
  • Modular manufacturing skids allowing for mobile units and smaller scale that can be used for cell gene therapy manufacturing

• Disadvantages
  • Cost
Data Integrity Issues and Hot Topics in FDA
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)
- Economic stressors– cutting corners
- Data review practices
- Increasing use of electronics systems 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
Current environment – risk for data integrity issues

- MHRA issued “GMP Data Integrity Definitions and Guidance for Industry” which has established an expectation that pharmaceutical manufacturers, importers and contract laboratories, as part of their self-inspection programme, must review the effectiveness of their governance systems to ensure data integrity and traceability.

- FDA Data Integrity and Compliance With CGMP Guidance for Industry
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 on in 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 for risk assessment
  - Less review and inspections
  - Look at overall state of facility
  - Ensure Quality and become patient centric
THANK YOU
Reference FDA Regulations

21 CFR
Title 21 Code of Federal Regulations (CFR)

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

• There are several Industry guidance documents that FDA uses. Check FDA website:

• Some Facility related guidance's
  • Changes to an approved NDA or ANDA
  • 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 product shall be of suitable size, construction and location to facilitate cleaning, maintenance, and proper operations.
    • Including adequate 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