How to Interact with the FDA/CDER when Designing Facilities?

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Outline

- Regulatory pathways when interacting with the FDA/CDER on facility/equipment design/upgrade
- Considerations/common issues when interacting with the FDA/CDER on facility/equipment design/upgrade

General Considerations

- Risk identification
  - Identify critical process steps based on scientific knowledge and knowledge of the process and product
- Risk Mitigation
  - Implement measures to reduce the risk in designing/redesigning, additional control measures, and/or changes in manufacturing procedures
- Contamination Control/Prevention
  - Advanced Manufacturing Technology to minimize direct operator interventions on the critical process.

How to interact with CDER when designing a new facility?

Interactions with FDA

- Pre-Operational Reviews (POR) of Manufacturing Facilities (FMD-135)
  - Review plans for construction of new or modifications of facilities prior to commercial production
- Emerging Technology Program (ETP)
  - Discuss, identify, and resolve potential technical and regulatory issues regarding the development and implementation of a novel technology prior to filing a regulatory submission
- Type C meetings
  - Discuss regulatory and technical issues regarding the development and review of a product

Pre-Operational Review (POR)

- To provide FDA guidance for construction of new or modifications of facilities prior to commercial production.
  - It provides FDA review and comments that may reveal defects early and prevent costly construction errors which could lead to defective operations and products.
  - Early HA's involvement with new or modified facilities will increase efficiency and result in the timely processing of applications and provide awareness of future work load obligations.
  - It is generally not product or application specific
- POR format: Face to face/virtual meeting or Written Response Only (WRO)
- Contact office: ORA Program area or CDER: CDER-OPQ-Inquiries@fda.hhs.gov

Pre-Operational Review

- POR reviews: Design and /or Pre-construction Review
  - Review of conceptual drawings, proposed plant layouts, and flow diagrams for the entire facility including critical systems and areas
    - HVAC, water systems, air pressure, air locks, flows
  - Emphasize the importance of the fundamental principles of good design as outlined in the CGMPs
- Recommendation:
  - The various packages of prints, specifications, design standards, and vendors' descriptions should be supplied in advance to permit meaningful review and comment prior to a meeting.
  - Identify specific questions or areas where FDA's comments are specifically desired and how the facility will meet CGMP requirements
  - Firms should be discouraged from presenting incomplete plans.
- Agency's participants:
  - Center CMC reviewers/Inspectors
  - ORA GMP Investigators

Pre-Operational Review

- Pre-Operational Visit (POV)
  - Firms may request FDA on-site review of specific portions of the facility
- Recommendation:
  - Request POV during the initial POR request
  - Provide regulatory and technical justifications to support the request
  - Seek feedback with examples of what they have seen at similar firms
  - Not recommended when a firm has an unacceptable compliance status
  - provide the firm with general feedback
    - Investigators are not consultants
- Agency's participants:
  - Center CMC reviewers/Inspectors
  - ORA GMP Investigators

What to Expect during a POR/POV?

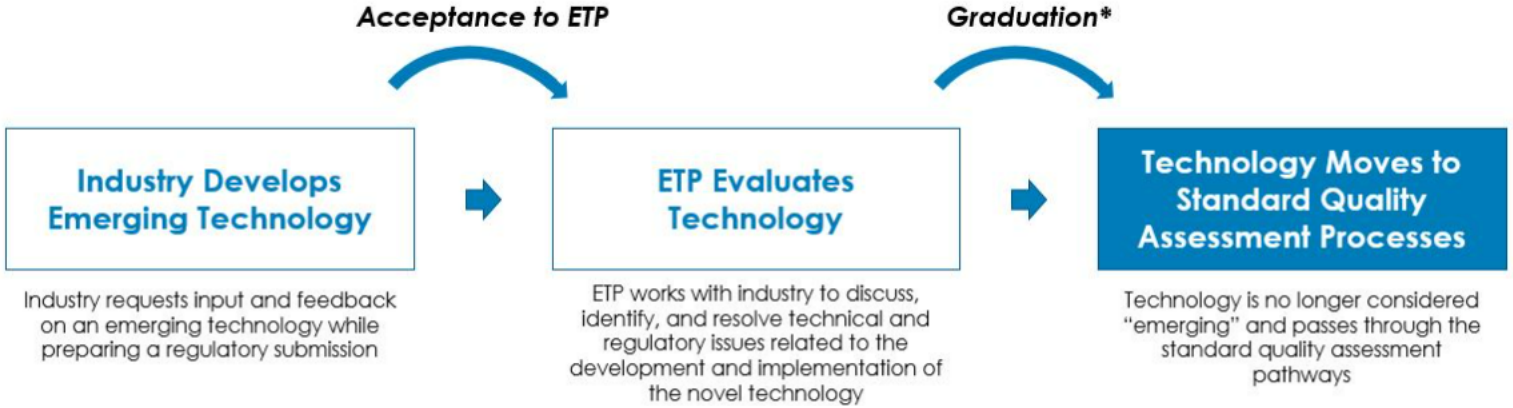
- All facility diagrams, site plans, personnel flow diagrams, etc. should be provided in advance of the meeting or on-site visit
- Focus on pre-defined questions
  - Questions regarding the design and control strategy
  - Technical and regulatory discussions regarding potential issues (“Red Flags”)
  - Potential risks for other products (clinical and commercial)
- A POR/POV does NOT guarantee approval or GMP compliance
- Not an inspection
  - No FDA 482, Notice of Inspection
  - No Establishment Inspection Report (EIR)
  - No FDA 483, Inspection Observations
- FDA meeting minutes/comments documented in a formal response within 30 days/WRO

Emerging Technology Program (ETP)

- Established in 2014, ETP is a collaborative program where industry representatives can meet with Emerging Technology Team (ETT) members to discuss, identify, and resolve potential technical and regulatory issues regarding the development and implementation of a novel technology prior to filing a regulatory submission.

- ETT members are representatives from all relevant FDA quality review and inspections programs including OPQ, CDER's Office of Compliance (OC) and the Office of Regulatory Affairs (ORA).

Emerging Technology Program (ETP)



Benefits to Participating in the ETP

- Pre-submission face-to-face/virtual interactions with ETT members and review staff to answer technical and regulatory questions during the development and adoption of a proposed technology.
  - Focus on the technology and its general applicability and do not need to be product specific.
- Regulatory and scientific input regarding what should be addressed in the CMC sections of a submission
- Assessment of emerging technology based on quality standards and policies that consider latest scientific advancement
- Partnering with relevant FDA offices involved in pharmaceutical quality to review and make recommendations on the approval of a regulatory submission
- Approvability of a new technology is a review decision under an application

How to Participate in the ETP?

- Technologies to qualify for participation in the Emerging Technology Program:
  - Have the potential to improve product safety, identity, strength, quality, and purity
  - Include element(s) subject to quality assessment for which the FDA has limited review or inspection experience, including an innovative or novel:
    - Product technology (e.g., dosage form or packaging such as a container and closure system)
    - Manufacturing process (e.g., design, scale-up or lifecycle approaches)
    - Control strategy (e.g., testing technology or process controls)

ETT Approach

- Early engagement
  - F2F/virtual interactions with ETT teams to provide scientific and regulatory input
- Integrated Quality Assessment (IQA)
  - ETT members: interdisciplinary IQA teams
- Emerging Technology Site Visit
  - Participation by OPQ and ORA members including ETT members
- Pre-approval inspections
  - Conducted by OPQ and ORA including ETT members

ETT Interactions

- Be transparent and willing to share with the agency early
- Not afraid to receive and answer questions from the agency
- Science and risk based assessments and decisions
- Willing to learn and understand new technologies
- A multi-disciplinary approach
- Potential questions
  - Technical and regulatory challenges?
  - Global harmonization?
  - New regulations?

Type C Meetings

- A Type C meeting is any meeting other than a Type A or Type B meeting between CDER and an applicant regarding the development and review of a product.
  - Request should be submitted to the applicant's application (e.g., IND, NDA, BLA)
    - When there is no application, the applicant should contact the appropriate review division
  - It should include adequate information for the FDA to assess the potential utility of the meeting and to identify FDA review staff
    - Requester can request agency's participants/divisions
  - Type C meetings should be scheduled to occur within 75 days of FDA receipt of the written meeting request.
    - F2F/virtual meeting or WRO

Information for Type C Meeting Request

- Product name and Application number (if applicable)
- Type of meeting being requested (i.e., Type A, Type B, or Type C)
- A brief statement of the purpose and objectives of the meeting
  - a brief background of the issues
  - a brief summary of completed or planned studies
- A proposed agenda and a list of proposed questions
  - Each question should be precise and include a brief explanation of the context and purpose of the question.
- A list of all individuals who will attend the requested meeting from applicant
- A list of FDA staff, if known, or disciplines asked to participate in the requested meeting
- Suggested dates and times for the meeting
- The format of the meeting (i.e., face to face, virtual, or WRO)

Potential Topics for Type C Meetings on Facility Design

- Facility improvement
  - New product introduction
  - SUS
- High risk process/products
  - High cross contamination risks
- Novel technologies
  - Robotic filling line
  - Continuous monitoring
  - Novel manufacturing process (CM for biotech)
- Follow up on FDA inspection observations

Common issues/considerations when interacting with the FDA

Expectations from FDA

- FDA general expectations
  - Identification of the facility (suite, line)
  - Proposed product(s) manufactured at the facility
    - Commercial and non-commercial
    - Product classes
  - Previous regulatory interactions
    - FDA or other HAs
    - Facility regulatory inspection history
  - Any available data from the proposed new facility/modifications

Expectations from FDA

- Technical and regulatory challenges
  - New technologies
  - Current regulatory expectations
- Provide sufficient background information and justifications
- Be specific, no open ended questions
  - Avoid questions already addressed in relevant guidances
- Focus on mitigating existing risks
- Provide rationales and justifications on potential regulatory challenges

Example of Questions when Interactions with FDA

- Does the Agency support the company's proposal to eliminate EM for viable samples during routine operations?
  - Company's position
  - Scientific and regulatory justifications
  - Risk assessment
  - Any additional supporting data?

Process and Product Considerations

- Understanding of process and products
  - Product types:
    - Chemical vs. Biological products
      - Biotech: growth promoting?
    - Potent/toxic products: ADE values
  - Process:
    - Microbial vs. Mammalian
    - Bioburden controlled vs. sterile process
    - Open vs. closed
    - SUS vs. SS
    - Pre-and post-viral segregations

Process and Product Considerations

- Facility and equipment requirements for upstream processes generally do not need to be as stringent for microbial fermentation as they do for mammalian cell culture.
- Establishments using completely closed systems may have less stringent room air quality requirements than establishments that do not.
  - Define closed systems?
- Establishments manufacture highly potent or toxic products or use spore-forming microorganisms
  - A comprehensive risk assessment relevant to the Facilities and Equipment system is expected.
    - Process Containment
    - Cleaning and Changeover

Microbial Contamination Considerations

- Three main microbial contamination considerations for the risk assessment:
  - Microbial Ingress: What are the sources of contamination and how are they gaining access to the manufacturing environment?
    - Open operations? Shared equipment? Raw materials? Flows? Operators? EM data?
  - Proliferation: Are there environmental factors or processing conditions that may increase the risk or extent of a contamination?
    - Growth promoting? Process hold times? Room Classifications?
    - DS: Bioburden control; DP: Sterility assurance
  - Persistence: Are the cleaning, sanitization/sterilization, and monitoring programs appropriate for all the product/contact equipment/systems to ensure bioburden is being eliminated or kept in check?
    - Cleaning/sanitization/sterilization validation? DHT/CHT/SHT? SUT/SS?

Cross-Contamination Risk Assessment

- Cross-Contamination Risk Assessment:
  - Microorganisms
    - Use animal-derived components
    - Microbial vs cell culture systems
    - Upstream and downstream operations
  - Segregation of live cell and cell-free areas and pre- and post-viral areas and to protect open operations
    - Pre- and post-viral activities
  - Potent/toxic products
    - A comprehensive quality risk management plan

Considerations for Highly Potent or Toxic Products

- Multiproduct facilities to manufacture highly potent or toxic products:
  - use appropriate risk management tools to assess cross-contamination risks
  - expected to have a quality risk management plan for cross-contamination
- Implement control strategies to mitigate cross-contamination and mix-up risks to acceptable levels.
  - use facility design, segregation, and process and procedural controls to control cross-contamination risks (SUS, single pass air, air sinks)
  - periodically review its risk management report for highly potent or toxic product cross-contamination to ensure that cross-contamination risks are continuously at an acceptable level
- Establish, based on toxicological data, the acceptable daily exposure (ADE) and to calculate the acceptance criteria for highly potent product residue for cleaning validation and verification.
  - Commercial and non-commercial products

Considerations for Highly Potent or Toxic Products

- Decontaminate/inactivate on shared product-contact equipment prior to cleaning
- Consider risks of cross-contamination through shared glass washers and CIP systems
- Analytical method sensitivities for cleaning validation to detect potent/toxic compounds
- Procedures in place for containing spills and decontaminating and cleaning areas and equipment affected by spills?
- Cleaning verification after cleaning shared product-contact equipment during each changeover
- Verify data for cleaning verification and requalification
- Cleaning verification for the share surface areas used to weigh and dissolve highly potent compounds

Common issues when upgrading an existing facility

- Lack of a holistic assessment on the existing facility/processes/products
  - Evaluate the changes for their potential impact on product quality
    - Change to water system, HVAC
    - Impact on area Pressure differentials?
  - Requalification following major changes
    - Changes in the equipment washing area
  - Cross-contamination risk assessment pre- and post- facility upgrades
    - Material, personnel, product, and waste flows
    - Viral segregations
    - Microbial vs. mammalian

Considerations for Equipment design

- Equipment design:
  - Use Restricted Access Barrier Systems (RABS) or isolators to minimize microbial contamination associated with direct human interventions
  - The use of different technologies should be based on process and product risks
    - Robotic environmental monitoring
    - Robotic filling operations
    - Comply with regulatory requirements?
- Single-Use Systems
  - Supplier/material qualification
  - Complexity of the assembly and manual operations
  - Leachables and Extractables
  - Leaks

Contact Information

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Thank You!