FDA Regulatory Perspectives on Multi-product Biological Facilities
CASSS CMC Strategy Forum

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Scope

• Regulatory framework for multi-product facilities
  – Requirements for single-product or dedicated facilities or areas
• Multi-product boundaries for adventitious agent and hazardous compounds
  – Cell substrates
  – Raw materials
  – Product categories
• Containment
  – Facility and equipment
• Procedural controls
  – Cleaning procedures
  – Change over procedures
• Summary
Regulatory Framework
The Desired State: A Mutual Goal of Industry, Society, and the Regulators

A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight.
FDA Initiative: Pharmaceutical Quality for the 21st Century—Risk-Based Approach

• Purpose of the initiative was to
  – Encourage adoption of new technological advances
  – Facilitate industry application of modern quality management techniques
  – Encourage implementation of risk-based approaches with focus on critical areas
  – Ensure regulatory review, compliance, and inspection policies are based on state of art pharmaceutical science
  – Enhance the consistency and coordination of FDA's drug quality regulatory programs
How do these initiatives relate to multi-product manufacturing?

• Directly applicable to multi-product manufacturing
  – Intended to provide manufacturing flexibility, efficiency and cost reductions while ensuring quality products through the
    • Acceptance of new technological advances, implementation of quality management techniques and risk management approaches
    • Implementation of consistent and coordinated review, compliance and inspection policies by the Agency
    • Key guidance documents ICH Q8, Q9, 10
    • Updated biological regulations 21 CFR 600.11(e) (2008)
More specifically…

- Traditional approach to biologics manufacturing has been relatively inflexible and costly
  - Use of dedicated facilities or areas for certain biological and potent compounds
  - Lack of comprehensive quality oversight
  - Lack of systematic risk management
  - Some flexibility for specified categories of biological product (Biotech products) with limits and regulatory oversight

- New initiatives are an opportunity to improve the efficiency, agility, and flexibility of the pharmaceutical manufacturing sector
Management of Risks

• ICH Q9 Risk Management
  – Key guidance
  – Provides for a holistic approach
    • Identify and understand risks for cross contamination
    • Implementation of appropriate risk control strategies
    • Level of effort should be commensurate with risks
Finished Pharmaceutical Regulations

• 21 CFR 211.42(c)
  – “There shall be separate or defined areas or such other controls systems for the firm’s operation as are necessary to prevent contamination or mix-ups……”
Regulations and guidances on use of single-product or dedicated manufacturing

- Regulations and guidances specifically address the following categories of products:
  - Penicillins and other beta lactam antibiotics
    - ICH Q7 4.4, 21 CFR 211.42
  - Products of infectious nature
    - ICH Q7 4.4, 21 CFR 211.42, 600.10(c)(3)
  - Product with high pharmacologic activity or toxicity (steroids, cytotoxic or anti-cancer agents)
    - ICH Q7 4.4, 21 CFR 211.42
  - Spore-forming microorganisms
    - 21 CFR 600.10(c)(3), 600.11(e)(3), 21 CFR 211.42
  - Live vaccines
    - 21 CFR 600.10(c)(4), 600.11(e)(4), 21 CFR 211.42
Building and Facilities

• 21 CFR 211.42 Design and construction features.
  – (d) “Operations relating to the manufacture, processing, and packing of penicillin shall be performed in facilities separate from those used for other drug products for human use.”
Recent draft Guidance on Manufacturing of Beta-Lactams

  – Separate buildings may not be necessary, provided that the section of the manufacturing facility dedicated to manufacturing penicillin is structurally isolated (completely and comprehensively separated) from the areas of the facility in which non-penicillin products are manufactured.
    • Under § 211.46(d), manufacturers must completely separate air handling systems for penicillin from those used for other drugs for human use.
    • Similarly, § 211.176 requires manufacturers to test non-penicillin drug products for penicillin where the possibility of exposure to cross contamination exists, and prohibits manufacturers from marketing such products if detectable levels of penicillin are found.
FDA guidance on penicillin and non-penicillin beta-lactams

• High risk
  • Difficult to define the minimal dose below which allergic responses are unlikely to occur
  • Lack of suitable animal or receptor testing models predictive of human sensitivity
  • Threshold dose at which allergenic response could occur is extremely low and
  • Difficult to detect with current analytical methods
  – These risk criteria could apply to other high risk products which could lead to facility dedication
21 CFR 600.11(e)(3) *Work with spore-forming microorganisms.*

- These regulations were recently revised and provide some manufacturing flexibility
  - (1) manufacturing processes using spore-forming microorganisms conducted in multi-product manufacturing site must be performed under appropriate controls to prevent contamination of other products and areas within the site.
  - Prevention of spore contamination can be achieved by a separate or dedicated building or by using process containment if manufacturing is conducted in a multi-product manufacturing building.
21 CFR 600.11(e)(4) *Live vaccine processing*

• These regulations were also revised recently (2008).
  – Emphasis was placed on the use of appropriate containment and control procedures.
    • (i)(A) “Use of a dedicated manufacturing area….”
    • (ii) “If manufacturing is conducted in a multi-product manufacturing building or area, using procedural controls, and where necessary, process containment”.
    • “Process containment is deemed to be necessary unless procedural controls are sufficient to prevent cross contamination of other products and other manufacturing areas within the building”.
    • “Process containment is a system designed to mechanically isolate equipment or an area that involves manufacturing using live vaccine organisms.”
      – *Emphasis is on procedural controls or process containment rather than facility dedication*
21 CFR 600.11(e)(4) Live vaccine processing (cont.)

- All product, equipment, and personnel movement must be conducted under conditions that will prevent cross contamination of other products and manufacturing areas. 
  - Intended to minimize mix-ups, cross over/carryover/mechanical transfers, and airborne cross contaminations

- Written procedures and effective processes must be in place to adequately remove or decontaminate live vaccine organisms from the manufacturing area and equipment for subsequent manufacture of other products.
  - Role of procedural controls such as cleaning and decontamination, viral inactivation, sterilization, etc.
Multi-product Facilities Boundaries
Manufacturing in Multi-product Facilities

• Concurrent manufacturing
  – Two or more products manufactured at the same time

• Campaign manufacturing
  – Two or more products manufactured on a campaign basis
    • Introduction of a second product carried out only after appropriate changeover
    • Staggered introductions
Types of Biological Manufacturing Facilities

• Multi-product
  – Campaign or concurrent manufacturing
    • More than one cell substrate
      – Same cell substrates (CHO cells)
      – Different mammalian cells (rodent and human)
      – Mammalian and microbial in same facility
      – Novel cell substrates
    • More than one product
      – Specified categories (biotech products)
      – Complex biologicals
      – Live vaccines
      – Potent/toxic/hazardous compounds
        » Occupational Exposure Limit (OEL) ≤ 10µg/m³
        » Acceptable Daily Exposure (ADE) ≤ 10µg/day
What is cross contamination?

- Contamination of a material or product with another material or product

- Any substance accidentally or unknowingly introduced into/onto a product (possibly rendering it harmful)
Avenues for Cross Contamination

- **Mix-ups**
  - Accidental error leading to the use of contaminated equipment or incorrect materials
  - Inadequate design of facilities and equipment
  - Inadequate procedural controls

- **Retention**
  - Inadequate cleaning
  - Product carryover
    - Residues from prior production activities
    - Product and non product surfaces
Avenues for Cross Contamination (cont.)

• Mechanical transfer or carry over
  – Transfer of contaminants from non-product contact surfaces into product
    • Operators/materials/equipment alternating between 2 or more processes or areas
    • Operator clothing and non-product surfaces

• Airborne Transfer
  • Uncontrolled release of dust, gases, sprays, or vapors from materials and product in the process
    – Migration of airborne particles throughout the production facility
    – Open vessels, poorly sealed process equipment, repeated transfers
FDA Expectations for Multi-product Biological Facilities

- Cross contamination risks must be addressed with a systematic risk management program
- Use of risk management principles described in ICH Q9
  - Applies to biological (adventitious agents) and chemical/biochemical (hazards) risks
- ISPE Baseline Guide: Risk-Based Manufacture of Pharmaceutical Products
  - Addresses risk from potent/toxic chemical compounds
  - No current agreement worldwide to the acceptable level of containment and procedural controls for potent/toxic compounds
    - Campaign manufacturing allowed or in dedicated facilities or isolators
- Where hazards are identified, controls must be multi-dimensional
  - Commensurate with risks
Reporting requirements for the conversion of single to multi-product manufacturing

- Major change requiring a PAS per 21 CFR 601.12(b):
  - Conversion of production and related area(s) from single to multi-product manufacturing area(s).
  - Changes in the location (room, building, etc.) of steps in the production process which could affect contamination or cross contamination precautions
Reporting requirements for the conversion of single to multi-product manufacturing (cont.)

• **Moderate change requiring a CBE-30 per 21 CFR 601.12(c):**
  – Manufacture of an additional product in a previously approved multiple product manufacturing area using the same equipment and/or personnel, if there have been no changes to the approved and validated cleaning and change over procedures and there are no additional containment requirements.

• **Minor change reportable in an annual report per 21 CFR 601.12(d):**
  – Change in the simple floor plan that does not affect production process or contamination precautions

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Guidance for Industry: Changes to an Approved Application for Specified Biotechnology and Specified synthetic Biological Products, 1997
Cell substrates
Regulations and guidances related to cell substrates

- 21 CFR 610.18 Cultures
- 1993 FDA Guidance on cell line characterization
- ICH Q5A and Q5D
- 2010 FDA CBER Guidance on Characterization and Qualification of Cell substrates and other Biological Materials Used in the Production of Viral Vaccines for Infectious Disease Indications
Cell substrates

- Different types of cell substrates can be used to manufacture biologicals and different risks can be identified with each type of cell substrate
  - Major regulatory concern is with mammalian cell lines, their susceptibility to adventitious agents and their potential to spread these agents in the manufacturing environment
  - Risks from the manufacture of products from multiple cell lines must be assessed and controlled
    - Implement appropriate containment and procedural control to prevent cross contamination, especially for open operations
    - Role of facility design and operation, equipment and process design in the containment of adventitious agents
      - Closed systems, vent filters on vessels, disposables, effective cleaning and sterilization methods
    - Specific viral inactivation/clearance methods
      - Methods should be based on known and potential viral contaminants and load
      - Methods should be updated and improved as new and improved manufacturing technologies and new analytical methods become available and adopted as industry standards
Facility Decontamination

• In the event of an viral contamination of a facility, it may be necessary to isolate the contaminated areas and decontaminate with hydrogen peroxide, chlorine dioxide or formaldehyde gas.
  – Firms should have a plan in place in the event of a viral contamination
Raw Materials
Raw Materials

- Include cell substrates, constituent materials, components, in-process materials, etc.
- Of concern those of animal origin or in contact with animal derived materials
  - Contaminations reported with bovine derived raw materials
    - Serum with Vesivirus 2117, Cache Valley virus (CVV) or infected with mycoplasma such as *Achloleplasma laidlawii*
- Important to consider
  - Role of facility design and operation, equipment, personnel, process and procedures in the prevention of cross contamination from raw materials
  - Specific raw material screening and pre-treatment methods should be in place for animal derived raw materials
    - Methods should be updated and improved as new and improved inactivation technologies and new analytical methods become available and adopted as industry standards
Regulatory Expectations for Raw Materials

• Some expectations
  – Eliminate of the use of animal derived materials, when possible
    • Remove use of serum from cell culture medium
  – Minimize use of biologically derived raw materials of high risk
    • Use certified animal derived raw materials
  – Conduct supplier audits
  – May need to handle biologically derived raw material (phytones, peptones, etc.) in segregated/dedicated areas and may need to be treated before use
  – Implementation of an effective testing program
Product categories
Product categories

• Biological products can encompass a wide variety of categories each with very different risk profiles
• Product categories encountered in multi-product biological facilities include:
  – Monoclonal antibodies, therapeutic recombinant proteins
  – Live vaccines, spore-forming microorganisms, infectious microorganisms
• Some biologicals have high pharmacologic activity or toxicity
  – Botulinum toxin, antibody drug conjugates, etc.
• These products can be manufactured in the same facilities used to manufacture other small molecules
  – Product with high pharmacologic activity or toxicity (steroids, cytotoxic or anti-cancer agents)
Product Categorization

• A risk management plan should be developed when dealing with potentially hazardous product of either biological or chemical nature
  – The purpose of the plan is to determine risk level and document acceptable risk
    • Categorize compounds
    • Determine acceptable risks for cross contamination
    • Develop strategies to mitigate risks
      – Help determine the level of containment
      – Procedural controls necessary to minimized risk of cross contamination
  – Risk is a function of hazard (potential harm) and exposure (e.g. acceptable daily exposure [ADE])
ADE for Product categorization

- Use toxicological and pharmacological data and clinical studies
- Acceptable Daily Exposure (ADE)
  - Dose unlikely to cause an adverse effect if an individual is exposed, by any route, at or below this dose every day for a lifetime
  - Used to determine acceptable limits for cross contamination and cleaning validation as well as worker safety.
  - Key is to control the level of exposure to the hazard
Containment
Facility Design

• Layout designed to allow for adequate process, material, personnel flow and to minimize potential of cross contamination through touch points and cross overs

• Segregation in the production areas
  – Spatial segregation for different operations
  – Separate AHU for different functional areas to prevent cross contamination, e.g., cell culture, pre-viral, post viral purification areas
  – Air flow from high to low area classification (except for live cell area, media and buffer area)
  – Room pressurization to maintain environmental cleanliness and prevent cross contamination
  – Use of closed isolators to contain hazardous compounds
  – Personnel, materials, and equipment with established SOPs and controls
  – Environmental monitoring to assess adequacy of contaminant controls
Expectations for Facility design

• Key facility factors in preventing contamination and cross contamination:
  – Overall facility design
    • Air handling system for segregation
    • Procedural separations of production activities (e.g., open)
  – Environmental control
    • Personnel flow, product flow, clean and dirty equipment flow
    • Use of closed systems
    • Personnel gowning practices
  – Disinfection
    • Effective cleaning and disinfection
Equipment

• In multi-product facilities
  – Product contact equipment is either
    • Dedicated or disposable
    • Shared (non dedicated)
    • Opened or closed

• Some containment features
  – Closed pipes & vessels with CIP/SIP capabilities
  – Closed sampling on vessels and pipes.
  – Maximize automated transfer to avoid manual connections; minimize manual open handling
  – Use in-line monitoring instrumentation to avoid frequent sampling.
Shared Equipment

• Cross contamination can be mitigated by using validated procedures for
  – Cleaning
    – Conducted to reduce specific residues
  – Sterilization or Sanitization
  – Chemical inactivation
Regulatory Expectations for Equipment

• Use of closed systems, when possible
• Focus on shared equipment
  – Cleaning and carryover
• Use validated CIP and SIP or other inactivation methods, as necessary
• Use disposables or dedicated equipment when effective cleaning, sterilization or sanitization is not feasible
  – Where a cross contamination cannot be contained
Procedural controls
Procedural Controls

• Critical to identify areas of potential cross contamination
  – Personnel gowning and training
  – Personnel and material flow
  – Equipment
    • Suitable cleaning procedures
      – reduce residues to or below a predetermined acceptable level
      – Use ADE to analyzed risk for a specific compound
      – ADE may be used used to derive swab or rinse limits for cleaning validation
  – Process
    • Use of validated adventitious agent inactivation methods
Cleaning validation

• Data to support cleaning when handling two products in the same facility

• Establishment of cleaning validation limits
  – Visibly clean
  – 1/1,000 of the lowest clinical dose (product A) in a highest daily dose of the next product (product B)
  – Not more than 10 ppm in the next product
    • May not be appropriate for highly hazardous compounds
  – Use of ADE for hazardous compounds
    • Setting a margin of safety based on toxicological data (ADE)
    • Determine the relationship between acceptance limits, actual cleaning data and the limit of detection of the method to set margin of safety based on ADE and safe threshold values
Changeover

• Before initiating a new campaign with a new product
  – Formal changeover process should occur
  – Major cause of product recalls
    • Inadequate line clearance between products
    • Use of dirty equipment
    • Use of wrong starting materials
    • Mislabeled equipment
    • Transfer of wrong products
Changeover

• Changeover should involve the following activities:
  – Personnel training and gowning
  – Materials, consumables, dedicated equipment and documents of previous process must be removed
  – Materials, consumables, dedicated equipment and documents for next process must be labeled and be available.
  – Shared equipment must be cleaned and cleaning verification must be conducted.
483 Observations
Biological Firm

• The XYZ manufacturing process has not been updated to reflect cGMPs. Current industry standards when manufacturing with animal derived cells calls for two orthogonal robust viral clearance steps. The XYZ process has only one robust viral clearance step.
Potent Compound Observations (Foreign API Manufacturer)

• Observation is paraphrased:
  – There was no written risk assessment to justify the facility, process, or operational design provisions, controls and containment strategies that are necessary to prevent cross contamination of other products with highly potent APIs (e.g., XX with an OEL of 0.1 µg/m³, YY with an OEL of 0.6 µg/m³, ZZ with an OEL of 0.4 µg/m³ and SS with an OEL of 2 µg/m³), nor is there any data to support the effectiveness of the current containment program for these products.
Warning Letter: Hazardous Compounds (Foreign Manufacturer)

- Your firm has not established separate or defined areas or such other control systems as necessary to prevent contamination or mix-ups during aseptic processing [21 CFR 211.42(c)]. For example,
  - Your firm lacked an adequate assessment of the cross-contamination risk posed by the manufacturer of several potentially hazardous compounds (e.g., beta lactam antibiotic and steroid product) at your facility. Deficiencies were observed in the shared manufacturing areas where you manufacture ophthalmic drug product intended for the US market. You should ensure that a documented justification and a well-designed contamination prevention strategy has been put in place to minimize the possibility of contamination. FDA encourages sound risk assessment approaches to address hazard identification, exposure consequences, and implement controls designed to prevent and detect cross-contamination. To achieve an acceptable level of risk requires sound and risk-based assurance that one drug does not contaminate another drug.
Summary

• FDA expects manufacturers to evaluate scientific data and implement the appropriate level of controls necessary to prevent the potential for cross contamination
• FDA evaluates risk management plans during GMP inspections
• Risk plan
  – Identify hazards
  – Manage risks
  – Address causes of cross contamination
  – Determine adequacy of control strategies
Summary (cont.)

- Cross contamination in multi-product facilities
  - Can be controlled by understanding the sources and nature of the potential adventitious agents or hazards
    - Involves risk management
  - Actions to control cross contamination may include
    - Managing opportunities for the spread or carryover of cross contaminants
    - Reducing carryover to acceptable levels where cross contamination is possible
    - Using new and sensitive analytical methods to monitor and control cross contamination, where feasible
    - Validating critical manufacturing steps to inactivate/remove adventitious agents to reduce cross contamination potential
    - Using dedicated facilities, areas or isolators, or other containment modes when cross contamination risks cannot be adequately mitigated
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