CBER’s Perspective on Regulating Raw Materials in Biologics

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Topic Covered

- CBER products
- Risks of adventitious agent contamination
- Qualification and management of raw materials
- Case study and control
- Regulatory Guidance documents
CBER Products

- **OVRR**
  - Vaccines
  - Allergenic extracts (for allergy shots and tests)

- **OCTGT**
  - Cell and gene therapy products
  - Human tissue and cellular products used in transplantation

- **OBRR**
  - Blood and blood components
  - Medical devices and test kits
Product Categories

- **Not Inactivated**
  - Live, attenuated virus vaccines
  - Allergenic extracts (pollens, foods, epidermoids, venoms)
  - Gene therapy vectors
  - Cellular therapy products
  - Tissue engineered products for regenerative medicine
  - Human Tissue and Cellular Products used in transplantation
  - Whole blood and plasma
  - Cellular blood products

- **Inactivated**
  - Whole virion and subunit vaccines
  - Allergenic extracts (molds)
  - Plasma derivatives
  - Recombinant proteins
  - Blood components
General Safety Concern

*Adventitious agents*

- **Acquired (Exogenous)**
  - infection in species of origin
  - cell culture passage history
  - handling or equipment
  - **raw materials** used in cell culture

- **Pre-exist as genetically-inherited sequences (Endogenous)** in cells used in production
Considerations for Development of a Comprehensive Testing Scheme for Product Safety

- **Assessing the risk of contamination**
  - Host species of origin
    - Health/medical history of donor
    - Naturally-occurring exogenous and endogenous viruses
    - Specific-exposure to other infectious agents
  - Product exposure history
    - Potential introduction of adventitious agents during manufacture due to
      - Handling
      - Raw materials
    - Cross-contamination in previous facilities *(if applicable)*
      - Propagation in different labs
      - Other viruses or cell lines used
      - Raw materials

- **Evaluating risk reduction**
  - Inactivation or clearance steps in the manufacturing process
  - Use of qualified reagents
Manufacturing Goals

- Product Safety
- High quality
- Lot-to-lot consistency
Adventitious agents may be introduced at many steps during product manufacture.
Generic Vaccine Production Scheme

Isolation of Vaccine Virus from tissue or cell culture

Amplification in Cell Substrate

Master Virus Seed

Working Virus Seed

(Parent Cell Bank)

Master Cell Bank

Working Cell Bank

VACCINE

End of Production Cells (Bank)

(Control Cells)
Considerations for Vaccine Safety

- **Characterization of cell substrate**
  - Cell phenotype: tumorigenicity may be associated with oncogenic viruses or DNA oncogenicity

- **Qualification of cell banks, virus seed and biological raw materials**
  - Extensive testing of vaccine virus seed and cell substrate
  - Use of raw materials certified or tested to be free of detectable virus

- **In-process testing**
  - Develop a comprehensive testing plan to evaluate bulk/production lots for known and novel viruses

- **Process validation**
  - Design an efficient process
    - to avoid risk of contamination
    - eliminate or reduce potential virus load
    - inactivate potentially contaminating virus

- **Reduction of residual host cell material in final product**
  - Whole cell removal
  - Cellular DNA and protein reduction
Raw Materials: Definition

- **Critical components for product manufacture**

  - **Cell lines and Eggs, Tissues, Biological Fluids** used for product manufacture

  - **Biological Materials** required for cell growth, differentiation, selection
    - Serum, trypsin, antibodies, media/media components, antibiotics, cytokines, growth factors, collagenase, DNase

  - **Chemical Materials** required for product purification
    - Polymeric matrices, buffers and solutions, hydrogels, processing components

  - **Physical Materials**
    - Mechanical supports, cell separation devices
Qualification of Raw Materials

- Source
- Identity
- Purity
- Safety
- Performance as desired/expected
Qualification Program

- Identification and selection
- Suitability
- Characterization
- Quality assurance
Management of Raw Materials

- Identification and selection
  - Suitability
  - Toxicity
  - Availability (alternate sources)
  - Consistency
  - Contamination
  - Traceability (especially for human- and animal-derived raw materials)
    - Donor infectious disease status (human)
    - Herd qualification and country of origin certification (FBS: during and after 1980)
Management of Raw Materials

- **Suitability for use in manufacturing:** effect on safety, potency and purity
  - Assess potential risk of toxicity and adventitious agents and their removal if using large amount during manufacture
Management of Raw Materials

Characterization

- Identity
- Purity
- Functionality
- Safety
  - Sterility
  - Endotoxin
  - Mycoplasma
  - Species-specific adventitious agents
    - 9CFR113 for animal-derived reagents
Management of Raw Materials

- **Quality Assurance**
  - Incoming receipt, segregation, inspection, and release of materials prior to use
  - Vendor auditing and certification
  - COAs verification testing or identity testing (as applicable)
  - Formal procedures and policies for out-of-specification materials
  - Stability testing
  - Archival sample storage
Control and Responsibilities

- **Source / Supplier**
  - Qualification / COAs
  - FDA-approved reagent

- **User / Manufacturer**
  - Audit Supplier
  - Testing materials directly or during production
  - Audit Testing Labs and results

- **Regulator**
  - Inspect Manufacturer
  - Review submissions
Cases of Virus Contamination due to Raw Materials

• **Serum**
  – **Bovine viruses:**
    • COMMON: BVDV, IBRV (bovine herpesvirus 1), PI-3, BLV, bluetongue virus
    • RARE: Reovirus, Cache Valley virus, epizootic haemorrhagic disease virus
  – **Equine viruses:** equine rhinitis A virus (ERAV) by genPCR, (2008; see below)

• **Trypsin**
  – Porcine parvovirus

• **Media components**
  – Minute virus of mice

• **Cells, Eggs, Tissues, Blood**
  – Indicator cells used in *in vitro* agent testing
    • ERAV due to equine serum (2008)
  – Blood components
    • West Nile Virus
    • Human Parvovirus B19 in Factor VIII
    • Hepatitis C in IGIV
Recent Case Study

2008: Chen et al., Biologicals 36, 393-402

- **OBSERVATION**
  - Vero cells used for bovine virus testing of a MCB by 9CFR 113 showed a positive result at day 19 subsequent to two subpassage of cells

- **IMPLICATIONS**
  - Low level contamination

- **POSSIBLE SOURCE OF CONTAMINATION**
  - MCB
  - Exogenously introduced during cell culture
    - Operator
    - Raw materials used in cell culture
Recent Case Study

- 2008: Chen et al., Biologicals 36, 393-402
  - INVESTIGATIONS
    - Retesting of MCB and parent banks - negative
    - Another concurrent, different assay using Vero cells was negative (28 d)
    - Characterization of contaminating agent
      - Replication and cell tropism studies
      - Microbiological assessment
      - IFA, detergent and low pH inactivation studies
      - EM, molecular characterization
  - IDENTIFICATION
    - Equine Rhinitis A virus (ERA V)
  - ROOT CAUSE
    - Fetal Horse Serum substituted routinely in 9CFR test for culturing Vero cells instead of FBS
Recent Case Study

- **2008: Chen et al., Biologicals 36, 393-402**
  - **FOLLOW-UP**
    - Horse serum used was not heat inactivated or gamma-irradiated, although tested free of detectable mycoplasma and microbes
    - Could not re-isolate ERAV by culturing Vero cells in 15% serum, even using a total of 50 ml serum
  - **IMPACT**
    - MCB was discarded by the manufacturer during the investigations as a precaution
    - Cloning and random primers were used to identify the contaminating agent and root cause
Efforts to minimize the risk associated with Biological Raw Materials

• Replace animal-derived materials
  – Serum-free cell cultures

• Use of new technologies for virus inactivation and removal

• Development of more sensitive and broad detection assays for adventitious agent detection and characterization to identify source
Product Safety

• Qualify Components
• Control the Manufacturing Process
• Characterize the Final Product
• Follow Recommendations in Relevant Guidance Documents
Some Relevant Regulatory Documents and Guidances

U.S. FDA

- Code of Federal Regulations (CFR):
  - 21 Part 610
  - 21 Part 211
  - 21 Part 630 (removed in 1996)
  - 21 Part 680
  - 9 Part 113 sections 53, 46, and 47

- PTC Characterization of Cell Lines Used to Produce Biologicals (1993)


- Guidance for Industry for Characterization and Qualification of Cell Substrates and Other Biological Starting Materials Used in the Production of Viral Vaccines for the Prevention and Treatment of Infectious Diseases (2006- Draft)

- www.fda.gov/cber/guidelines.htm
Some Relevant Regulatory Documents

ICH

- Q5D Derivation and Characterization of Cell Substrates Used for Production of Biotechnological/Biological Products

- Q5A Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin

WHO

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