Unexpected Finding of Adventitious Agent in a Biological Product: A Regulatory Perspective

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Manufacture of Biological Products

Manufacture of a large class of biological products, including vaccines and cell and gene therapy products, often requires use of cell substrates and raw materials of animal origin.

Potential risk that cell substrates and raw materials can be contaminated with adventitious agents (endogenous or exogenous)

Adventitious Agents

- Adventitious agents can be viruses, bacteria, mycoplasma, fungi, rickettsia, protozoa, parasites, and TSE agents.
- Potential concern that adventitious agents can be unintentionally introduced into the manufacturing process

Biological Products: Purity

Purity: 21 CFR 610.13 states in part that "Products shall be free of extraneous material except that which is unavoidable in the manufacturing process described in the approved biologics license application."

Stringent regulatory requirements in place to ensure, to the extent possible, that products are "free" of adventitious agents.

Biological Materials Used for Product Manufacturing

Manufacturing processes for many biologics involve use of cells, tissues, and animal-derived raw materials that have the potential to introduce adventitious agents into the product.

Possible Sources of Contamination e.g., for Viral Vaccine

- Human patient or animal that was source of initial virus isolate
- Cell substrates (used for isolation, attenuation, propagation of virus)
- Animal derived raw materials used during manufacturing (e.g., serum, trypsin)
- Personnel handling or equipment

Approaches for Detection of Adventitious Agents

- Adventitious agent testing utilizes a combination of methods and strategies and is performed at various stages during the manufacturing process.
  - Use of multiple strategies for testing provides assurance, to the extent possible, that products are “free” from adventitious agents.
  - Testing is performed at multiple steps during manufacturing process to maximize chance of detecting contaminant.
- Requirement for cGMP to ensure high quality products

Adventitious Agent Testing of Products, Intermediates, and Raw Materials

Testing performed on:

- Cell substrates used during manufacturing (Master, Working, EOP)
- Virus seeds (Master, Working)
- Final Bulk Product
- Final Filled Product
- Animal derived raw materials

Current Methods for Detection of Adventitious Agents

- Broad, overlapping schemes used to detect as wide an array of adventitious viruses as possible
- Non-specific methods used to detect known and unknown agents
  - *In vivo* methods (adult and suckling mice, embryonated hens' eggs, guinea pigs, rabbits)
  - *In vitro* methods (cell culture)
  - Molecular/biochemical assays
- Specific methods to detect known agents
  - Molecular techniques e.g., PCR

CBER Guidance Document

Guidance for Industry: "Characterization and Qualification of Cell Substrates and Other Biological Materials Used in the Production of Viral Vaccines for Infections Disease Indications" (March 2010)

http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/UCM202439.pdf

Additional testing may be required depending on product history (determined on case-by-case basis).

New technologies have the potential to detect *adventitious agents not previously known or detected* in cell substrates and biological products.

Introduces *scientific and regulatory challenges* that must be addressed on a case-by-case basis

Historical Perspective: Examples (1)

SV40 in inactivated poliovirus vaccine

- Formalin inactivation did not completely inactivate SV40
- SV40-free IPV was produced as quickly as possible
- Licensure of OPV was delayed until SV40 free preparation could be made

EAV in egg-derived vaccines

- More sensitive PCR assay (PERT) showed that previously undetectable quantities of reverse transcriptase (RT) were present in some vaccines (e.g., measles) produced in avian cells
- Studies determined PERT test was detecting RT from defective endogenous avian retrovirus (EAV) particles which do not induce productive infections in culture.
- Long safety record of vaccines produced in these substrates was important consideration

Historical Perspective: Examples (2)

TSE and vaccines

- Concern raised that use of bovine derived materials sourced from countries with BSE or at risk of BSE could pose theoretical risk of TSE in vaccine recipients
- CBER issued letters to manufacturers requesting information on sourcing of all bovine-derived materials used during vaccine production
- For products with potential exposure to bovine derived materials from countries which either have or may have BSE, risk assessments were performed, based on maximum possible exposures, dilution factors, potential infectious doses, etc.

Historical Perspective: Examples (3)

TSE and vaccines (con't)

- CBER convened joint meeting of the TSE Advisory Committee and Vaccines and Related Biological Products Advisory Committee to seek expert guidance on potential TSE risk from bovine-derived materials
- Concluded risk of vCJD was theoretical and remote, and benefits of vaccination far outweigh any remote risk of vCJD
- To remove even a theoretical risk, CBER recommended manufacturers not use bovine-derived materials from countries which either have or may have BSE.
- Many Working Virus Seeds were re-derived to eliminate potential concern regarding TSE.

Unexpected Finding of Adventitious Agent in Licensed Vaccine – Recent Experience

- Using metagenomic technology, investigators at UCSF detected DNA sequences originating from porcine circovirus (PCV-1) in two batches of Rotarix (GSK's live attenuated rotavirus vaccine); CBER and GSK confirmed results
- RotaTeq (Merck's live attenuated rotavirus vaccine) was tested by the manufacturer and CBER for potential PCV contamination; fragments of PCV-1 and PCV-2 DNA were detected in RotaTeq

Case Study: Rotarix and PCV-1

- Utilizing novel technology, academic investigators detected PCV-1 in Rotarix
- Tests confirmed presence of PCV-1 DNA in Master and Working Cell Banks, Virus Seed, Intermediates in production process, and Final Container
- PCV-1 was present in the vaccine from the earliest stages of product development (MCB, WCB, Virus Seed), and in the vaccine lots used in clinical trials (Phase 1, 2, and 3).

Rotarix and PCV-1: Evaluation of Potential Risk (1)

Important considerations:

- **PCV-1 not known to infect or cause disease in humans; PCV-1 does not cause disease in animals**
- **PCV-1 was present in vaccine lots from early stages of development; safety data from large clinical trial database (71,209 infants enrolled in 8 clinical studies; 36,755 received Rotarix and 34,454 received placebo)**
- **Extensive post-licensure safety experience (> 69 million doses)**
- **Demonstrated benefit of vaccine against morbidity and mortality caused by rotavirus**

Rotarix and PCV-1: Evaluation of Potential Risk (2)

CBER and GSK conducted studies to further characterize the contaminant. **Fundamental scientific questions:**

- Is PCV-1 DNA in Rotarix particle-associated or present as nucleic acid fragments?
- Does the PCV-1 DNA represent full-length genomes?
- If full length and particle associated, are the particles replication competent in a permissive cell line? In human cell lines?
- If replication competent in cell culture, any evidence of PCV-1 infection in subjects who were immunized with Rotarix (seroconversion? detection of PCV-1 in stool?)
- How many PCV-1 genome copies are present per dose?

Rotavirus Vaccines and PCV: Evaluation of Potential Risk (3)

Rotarix: **Results of studies done by CBER and GSK:**

- **PCV-1 DNA in Rotarix is particle associated, and represents near full length DNA; particles are replication competent in cell culture.**
- **No evidence that PCV-1 replicated in the human host (no seroconversion; PCV-1 DNA detected in stool of some subjects but timing relative to vaccination suggests transient passage of PCV-1 through GI tract of host).**

RotaTeq: **Results of studies done by CBER and Merck:**

- **PCV-1 and PCV-2 DNA fragments are present in Rotateq**

Rotarix and PCV-1: Open Public Discussion

- CBER sought external scientific input on finding of PCV-1 in Rotarix from the Vaccines and Related Biological Products Advisory Committee (VRBPAC).
- Findings regarding presence of PCV-1 and PCV-2 DNA in RotaTeq too preliminary at time of VRBPAC meeting to discuss; finding was noted in CBER's presentation

Rotavirus Vaccines: Conclusions

Based on all available information and feedback from the Advisory Committee, CBER concluded:

- Safety of rotavirus vaccines (Rotarix and RotaTeq) is supported by available data
- Benefits of the vaccines, which are known, are substantial and outweigh the risk, which is theoretical
- Use of rotavirus vaccines can continue

Rotavirus Vaccines and PCV: Actions Taken and Next Steps

- Product labels revised to include information about presence of PCV-1 in Rotarix, and presence of PCV-1 and PCV-2 DNA fragments in RotaTeq
- GSK plans to rederive vaccine, in consultation with CBER, to manufacture Rotarix that is free of PCV-1
- CBER evaluating implications for other licensed vaccines

Rotavirus Vaccines and PCV: Communications and Transparency

- CBER had frequent communications with the public to share information, as it became available, and to maintain transparency during investigation process.
- CBER maintained close communications with international partners (WHO, EMA, other NRAs) to discuss steps being taken to evaluate and address findings of PCV-1 in Rotarix.

Communication and transparency critical during investigation and decision making process

Regulatory Considerations

Regulatory considerations in decision-making process:

- **Is there a known risk or is it a theoretical risk?**
- **What are the clinical implications (any safety concerns regarding the agent)?**
- **What is the safety record of the product from clinical trials, controlled post-marketing observational studies, and post-marketing passive surveillance (e.g., VAERS reports)?**
- **What is the benefit/risk profile for the product? (Benefit/risk determination must be made for each region or country.)**

Other questions considered on a case-by-case basis

New Technologies and Discovery of Novel Viruses: Regulatory Implications

- Detection methods for adventitious agents continue to evolve and improve; new methods may have higher sensitivity and throughput
- Novel viruses (not previously known) being discovered; could be present in existing or new cell substrates and biological products
- New technologies could allow detection of previously unknown or undetectable agents
  - May further support safe product development
  - Present regulatory challenges

Use of New Generation Molecular Methods

Issues to Consider:

- Sensitivity?
- Requirements for standardization? What are appropriate standards?
- Breadth of adventitious agents detected?
- Reproducibility and robustness of method?
- Commercial feasibility?

Results may require further follow up to determine significance.

CBER's Approach to Addressing Unexpected Finding in Licensed Product:

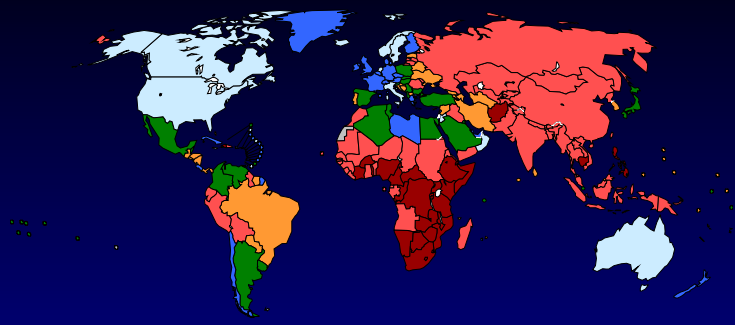
- Investigate and assess the findings: Evaluate available scientific data; conduct studies, if appropriate; communicate with manufacturer and provide guidance regarding investigation plan, if needed
- Seek guidance from external Advisory Committee, if needed
- Maintain transparency regarding investigation process and keep clinicians, health care providers, and public informed
- Communicate with international colleagues to share information and harmonize efforts among various National Regulatory Authorities to address issue
- As appropriate, develop plan to produce product without adventitious agent at the earliest opportunity

Adventitious Agents: A Continuing Challenge

Regulatory decisions based on sound science, assessment of all available data, and risk/benefit considerations

Evaluated on case-by-case basis

FDA's Strong Commitment to Global Public Health



- FDA is actively engaged in assuring the safety, effectiveness, and availability of products that touch so many lives and are critical for public health and preparedness.
- Emerging threats, technologies, and opportunities demand constant renewal of scientific expertise and capacity.
- The challenges and opportunities for leadership and public health are truly global – communication and collaboration are key to successful partnership.