Production Assistance for Cellular Therapies

Welcome to the

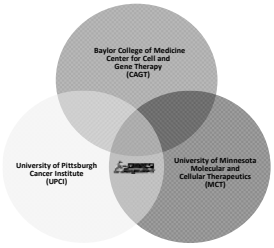
Educational Web Seminar
Deviation Management of Type 351 and 361 Cell Products

Thursday July 16, 2009
12:00 Noon - 1:00 PM ET

The presentation slides for this web seminar are available publicly on the main web page at:
www.pactgroup.net

PACT

A National Heart Lung and Blood Institute-funded initiative



- PACT manufactures quality cell therapy products on behalf of investigators with funded clinical trials requiring support in product development
- PACT's educational training focuses on three general areas: translational development/scale-up and manufacture of cell therapy products, quality assurance, and regulatory issues
  - Workshops (onsite)
  - Web Seminars

National Heart Lung and Blood Institute
People Science Health

Today's Education Web Seminar

"Reporting Deviations of Biological Products and HCT/Ps "

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Web Seminar

Description

This web seminar will provide an overview of the regulatory pathways for reporting, manufacturing and/or testing product deviations in Type of 351 and 361 products. Product deviation management scenarios will be presented and discussed.

Objectives

- Compare the different deviation reporting pathways for 351 and 361 products
- Interpret the regulatory requirements and the documentation expected by various professional standard setting organizations regarding product deviation management procedures
- Develop and apply appropriate procedures for reporting product deviations to regulatory agencies for your facility

Faculty Disclosure

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of AABB and PACT. AABB is accredited by the ACCME to provide continuing medical education for physicians. In accordance with the ACCME Standards for Commercial Support[sm], all faculty for this event have signed a conflict of interest form in which they have disclosed any significant financial interests or other relationships with the industry relative to the topics they will discuss during this program.

Faculty Disclosure Information

Faculty	Disclosure	Nature of Relationship	Manufacturer/Provider
Ellen Areman	None	non-PACT member	
Lisa Davis	None	PACT member	
Nathan Kassalow	None	PACT member	
Karin Quinnan	None	PACT member	
David Styers	None	PACT member	
Debbie Wood	None	PACT member	

Reporting Deviations of Biological Products and HCT/Ps

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Relevant Legislation

- Public Health Service (PHS) Act
  - Regulates biological products
  - Section 351 defines "biological products"
    - » Posing higher health risk
    - » May be approved as licensed biologic by FDA
    - » Must comply with subparts B, C and D of 1271 regulations
  - Section 361 applies to HCT/Ps
    - » Posing lower health risk than "351" products
    - » Purpose is to prevent the introduction, transmission, or spread of communicable diseases
    - » No pre-market review
    - » Meet criteria in 1271.10

Purpose of PHS Act

- Prevent unwitting use of contaminated HCT/P products
- Prevent improper handling or processing that might contaminate HCT/P products
- Ensure that clinical safety and effectiveness are demonstrated for biological cells and tissues ("351" products)

Human cells, tissues, and cellular and tissue-based products (HCT/Ps) - Definition

- Articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer to a human recipient

Examples of HCT/Ps

- Musculoskeletal tissue
- Skin
- Ocular tissue
- Human heart valves
- Dura mater
- Reproductive tissue
- Hematopoietic stem/progenitor cells
- Other cellular therapies
- Tissue/device and other combination therapies

Criteria for Regulation Solely Under Section 361 of the PHS Act

1. Minimally manipulated
2. Intended for homologous use
3. Not combined with another article; and
4. No systemic effect and not dependent on metabolic activity of living cells
   - Exceptions: autologous use; use in a first- or second-degree blood relative

What's Left?

- Any cellular therapy product that doesn't meet all 4 criteria
  - More than minimally manipulated (highly processed)
  - Not intended for homologous use
  - Combined with another article; or
  - Systemic effect and dependent on metabolic activity of living cells

What is a Product Deviation?

- HCT/P deviation (21 CFR 1271.3(dd) :
  - A deviation from applicable regulations in this part or from applicable standards or established specifications that relate to prevention of **communicable disease transmission** or **HCT/P contamination**; or
  - An unexpected or unforeseeable event that may relate to the transmission/potential transmission of a communicable disease or may lead to HCT/P contamination
- Biological product deviation (§600.14)
  - Event associated with manufacturing, holding, or distribution of licensed product if it represents a deviation from CGMP, applicable regulations and standards, or specifications that may affect **safety, purity, or potency** of the product

Requirements for BPD Reporting

- Different requirements for different situations
  - 351 Products – Investigational
  - 351 Products – Licensed
  - 361 Products

Who Must Report

- 351 products under IND
  - IND holder
- 351 licensed biologics
  - Manufacturer that holds the license
- 361 HCT/P
  - Establishments that manufacture HCT/P

Definition—Manufacture

- Manufacture means any or all steps in the recovery, processing, storage, labeling, or distribution of any human cell or tissue, and the screening or testing of the cell or tissue donor

What to Report - 351 Products Under IND

- No specific IND deviation reporting requirements
- Report deviations that occur in manufacture of unlicensed material used as part of IND
  - IND Safety Reports & Annual Reports
- "Any unexplained discrepancy… or the failure of a batch or any of its components to meet any of its specifications shall be thoroughly investigated, ***whether or not the batch has already been distributed***… A written record of the investigation shall be made and shall include the conclusions and follow-up." (§ 211.192)

What to Report - 351 Licensed Biologics

- Report "any event associated with manufacturing … or with holding or distribution of a licensed biological product, in which the safety, purity, or potency of a distributed product may be affected"
- Use Form FDA 3486, Biological Product Deviation Report
- Manufacturer must report deviations that occur in own facility or in a facility under contract with the manufacturer

What to Report - 361 HCT/Ps

- Deviation from applicable regulations or standards or from established specifications relating to prevention of communicable disease transmission or HCT/P contamination
  - Deviation from **core CGTPs** in 21 CFR 1271.145 & 150
- Unexpected or unforeseeable event that may relate to the transmission or potential transmission of a communicable disease or may lead to HCT/P contamination.
- Manufacturer must report whether deviation occurred in own facility or in facility that performed a manufacturing step under contract, agreement, or other arrangement

CGTP Core Requirements

- Requirements most directly related to preventing introduction or transmission or spread of communicable disease

When to Report

- HCT/P - 21 CFR 1271.350(b)(3) – Within 45 days of discovery of event
- Biologics – 21 CFR 600.14(c) – As soon as possible, but not to exceed 45 calendar days from the date you acquire information reasonably suggesting that a reportable event has occurred

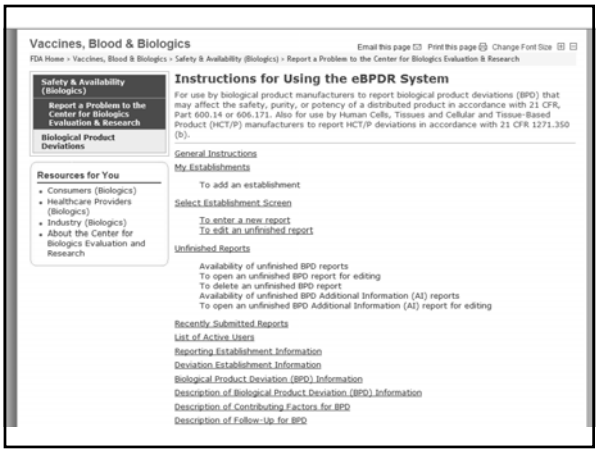
How to Report – Standardized Reporting Format

- Submit electronically or in paper form by mail [Form FDA 3486]
- Instructions include
  - List of biological product deviation codes
  - List of blood product codes
  - List of non-blood product codes

Form FDA 3486

The eBPDR System

- For use by biological product manufacturers to report biological product deviations (BPD) that may affect the safety, purity, or potency of a distributed licensed product (21 CFR, Part 600.14 or 606.171).
- Also for use by Human Cells, Tissues and Cellular and Tissue-Based Product (HCT/P) manufacturers to report HCT/P deviations [21 CFR 1271.350(b)].



CGMPs vs. Core CGTPs

- CGMPs
  - Organization and Personnel
  - Buildings and Facilities
  - Equipment
  - Control of components, containers and closures
  - Production and process controls
  - Holding and distribution
  - Laboratory controls
  - Records and reports
- Core CGTPs
  - Facilities
  - Environmental Control
  - Equipment
  - Supplies/Reagents
  - Processing/Process Controls
  - Labeling Controls
  - Storage
  - Receipt, Predistribution, and Distribution
  - Donor Eligibility

Deviation Codes

- **Non-Blood Codes**
  - IM - Incoming Material Specifications
  - PC - Process Controls
  - TE - Testing
  - LA - Labeling
  - PS - Product Specifications
  - QC - Quality Control and Distribution
  - MI - Miscellaneous
- **HCT/P Codes**
  - DE - Donor Eligibility
  - DS - Donor Screening
  - DT - Donor Testing
  - EC - Environmental Controls and Monitoring
  - SR - Supplies and Reagents
  - RE - Recovery
  - PC - Processing and Process Controls
  - LC - Labeling Controls
  - ST - Storage
  - SD - Receipt, Pre-Distribution, Shipment and Distribution

BPD Code XX-YY-ZZ

- BPD Code made up of 3 levels
  1. (XX) identifies system in which there was breakdown or failure, resulting in distribution of an unsuitable product.
     Ex: PC – Process Controls
  2. (YY) is subset of system affected
     Ex: PC-21 - Manufacturing or processing performed using incorrect parameters
  3. (ZZ) contains more detailed information
     Ex: PC-21-02 – Incorrect temperature

Examples of BPDs (351 products)

- Container or closure does not conform to written procedures or is defective
- Source material does not meet specs
- Process controls not followed
- Testing not performed or performed incorrectly
- Labeling
  - Incorrect information on label or package insert

Examples of BPDs (361 products)

- A reagent was used that was not verified for sterility
- Product was stored above allowable temperature
- HCT/P microbial detection testing came up positive after product was distributed
- An inappropriate kit was used for donor testing

Scenario 1

- Frozen **autologous** peripheral blood progenitor cell product transported from the Cell Therapy Lab to patient care unit for infusion. Product placed in water bath for thaw. During the thawing of product bag a small leak was noticed by the technologist. The bag was clamped and the cells were transferred to another bag. A sterility sample was removed from the bag and the cells were infused with permission from the Laboratory Medical Director and patient physician. **Sterility testing from the bag was negative** for microorganisms.

Scenario 2

- **Unrelated cord blood under IND** is received by transplant hospital. Upon thawing the cord blood unit in the laboratory routine ABO/Rh testing is performed on the product. The ABO/Rh **results do not match** the type reported by the Cord Blood Bank. The unit is not infused and subsequent investigation determines that the unit was mislabeled with results of another cord blood unit.

Scenario 3

- During the manufacturing of an **autologous** tumor vaccine in a Class 10,000 clean room the air handling system shutdown for 4 hours. Due to **urgent medical need** production was continued and the product was infused. All Lot Release testing passed including gram stain testing (taken after air handler shutdown). Approval for release obtained from the Lab Medical Director and Principle Investigator prior to issuance of the product. Environmental monitoring performed during shutdown was outside of acceptable limits. 14 day **sterility testing** of product was **negative**.

Adverse Reaction Reports (21 CFR 1271.350)

- Manufacturers must investigate any adverse reaction involving a communicable disease related to an HCT/P they made available for distribution if the reaction was
  - Fatal
  - Life-threatening
  - Caused permanent damage
  - Necessitated medical or surgical intervention

Comparison of Reporting Requirements

- Adverse Event Reporting
  - 15 days from receipt of info
  - Reported by facility that made HCT/P available for distribution
  - FDA form 3500A (Medwatch)
- BPD Reporting
  - 45 days from receipt of info
  - Reported by manufacturer
  - FDA Form 3486

Remember

You Don't Need to Report to FDA if*

- 351 Products
  - The affected biological product was not distributed
  - The occurrence was detected and corrected prior to distribution of the product
  - The occurrence did not affect safety, purity or potency of the licensed biologic.
- 361 Products (HCT/Ps)
  - The affected HCT/P was not distributed
  - The occurrence was detected and corrected prior to distribution of the product
  - The occurrence was not related to transmission of communicable disease or product contamination
  - The occurrence is not related to core CGTPs

*You should still investigate and document all deviations

References

- Food and Drug Administration. Current good tissue practice for manufacturers of human cellular and tissue-based products; inspection and enforcement; final rule. Fed Regist 2004;69:68612-88.
- Guidance for Industry: Biological Product Deviation Reporting for Licensed Manufacturers of Biological Products Other than Blood and Blood Components. Oct. 2006
- Areman EM and Loper KL, eds. Cellular Therapies: Principles, Methods and Regulations – AABB Press. 2009. In press.

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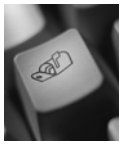

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CME Information

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CME Credit

If you are interested in obtaining CME credit for attending this web seminar, please note that each attendee must:

~Sign and fax roster to 240-306-2527~

~Complete the online survey~

PACT Web Seminar #14 Survey

(Survey link above embedded in the reminder email sent Wednesday, July 15th)

Note: Please complete within 48 hrs of the web seminar

AABB Live Learning Center

After the rosters have been processed, you will receive an email from AABB with instructions on how to print your CME/CE certificates for this web seminar

Thank you for attending!

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