

***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

Adobe Acrobat Professional - [Form3486.pdf]

File Edit View Document Tools Advanced Window Help

Save As. Print Next Page Reset Form

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION

**BIOLOGICAL PRODUCT DEVIATION REPORT**

\* Indicates required information

A. FACILITY INFORMATION		B. BIOLOGICAL PRODUCT DEVIATION (BPD) INFORMATION	
<b>1. Reporting Establishment Information</b>		1. Establishment Tracking #	
* Reporting Establishment Name		2. Date BPD Occurred	
* Street Address Line 1		3. * Date BPD Discovered	
Street Address Line 2		4. * Date BPD Reported	
* City	* State	5. * Description of BPD (use Page 2 for additional space) <a href="#">Go To Page 2</a>	
Country	* Zip Code	6. * Description of Contributing Factors or Root Cause (use Page 3 for additional space) <a href="#">Go To Page 3</a>	
* Point of Contact		7. * Follow-Up (use Page 4 for additional space) <a href="#">Go To Page 4</a>	
* Telephone # ( )		8. * Please Enter the 6 Character BPD Code	
E-mail			
<b>2. * Reporting Establishment Identification Number</b>			
FDA Registration #			
CLIA #			
<b>3. If the BPD occurred somewhere other than the above facility, please complete this Section and Section A4, otherwise continue onto Section B1.</b>			
* Establishment Name			
Street Address Line 1			
Street Address Line 2			

FDA USE ONLY	
Date Received:	
Date Reviewed:	
BPD ID:	
BPD No.:	

8.5 x 11 in

1 of 8

# *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)].



### CBER On-Line - Login Screen

Use the CBER On-line system to make these electronic submissions online:  
Blood Establishment Registration (Form FDA 2830)  
Tissue Establishment Registration (Form FDA 3356)  
Biological Product Deviation Reporting (Form FDA 3486)

New CBER On-Line Users  
New users must first create an account. [Create a New Account](#).

If you need further assistance e-mail us with your account information: [Contact CBER On-Line Technical Support](#)

Existing account holders may login by entering your user name and password below.

Create New Account

See Instructions

Contact Support

\*User Name:

\*Password:

[Forgot your User Name or Password?](#)

\*Application:

CBER On-Line - Main Menu



**REMINDER:** User Names and Passwords are CASE SENSITIVE

LOGIN

\*Required

[Help](#)

CBER On-Line Version 1.8.0

**Safety & Availability  
(Biologics)**

**Report a Problem to the  
Center for Biologics  
Evaluation & Research**

**Biological Product  
Deviations**

### Resources for You

- [Consumers \(Biologics\)](#)
- [Healthcare Providers \(Biologics\)](#)
- [Industry \(Biologics\)](#)
- [About the Center for Biologics Evaluation and Research](#)

## Instructions for Using 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 product in accordance with 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 in accordance with 21 CFR 1271.350 (b).

### [General Instructions](#)

### [My Establishments](#)

[To add an establishment](#)

### [Select Establishment Screen](#)

[To enter a new report](#)

[To edit an unfinished report](#)

### [Unfinished Reports](#)

[Availability of unfinished BPD reports](#)

[To open an unfinished BPD report for editing](#)

[To delete an unfinished BPD report](#)

[Availability of unfinished BPD Additional Information \(AI\) reports](#)

[To open an unfinished BPD Additional Information \(AI\) report for editing](#)

### [Recently Submitted Reports](#)

### [List of Active Users](#)

### [Reporting Establishment Information](#)

### [Deviation Establishment Information](#)

### [Biological Product Deviation \(BPD\) Information](#)

### [Description of Biological Product Deviation \(BPD\) Information](#)

### [Description of Contributing Factors for BPD](#)

### [Description of Follow-Up for BPD](#)

# 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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