

BIOLOGICAL PRODUCT DEVIATION REPORTING



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Objectives

- Define a biological product deviation (BPD)
- Identify the criteria for determining when establishments must report BPD events to the FDA
- Describe how BPDs should be reported to the FDA
- BPD scenarios; Is it reportable?

“To err is human; to admit it, superhuman”

– Doug Larson

What Is a BPD?

Biological Product Deviation

- Defined by the FDA as any event that represents a deviation from cGMP, applicable regulations, applicable standards, or established specifications that may affect the safety, purity or potency of the product involved
- **AND** the deviation occurred in your facility or in a facility under contract with you
- **AND** the deviation involves distributed blood or blood components.

BPD Reporting History

- Originally only licensed establishments were required to report (21 CFR 600.14(a))
- 1991 Memo requested voluntary reporting from unlicensed registered blood establishments and transfusion services
- 2000 Final Rule amended cGMP regulations and required all to report (21 CFR 606.171)
- 2001 Draft Guidance finalized in 2006

21CFR 606.171

- Effective 5/7/2001
- Requires reporting by all unlicensed blood establishments, including transfusion services and registered blood banks
- Replaces “error and accident” terminology with “biological product deviation”
- More clearly outlines the types of events that require reporting
- Limits reporting to those events that may affect safety, purity, or potency of distributed products
- Establishes a reporting timeframe of 45 days from the date the event was discovered

Guidance for Industry

GUIDANCE DOCUMENT

Biological Product Deviation Reporting for Blood and Plasma Establishments

Guidance for Industry

OCTOBER 2006

[Download the Final Guidance Document](#)

[Read the Federal Register Notice](#)

Final

Guidance Requirements

FDA's Recommendations For Investigations of Unexplained Discrepancies or Failure of Lot/Unit to Meet Specifications

What is required of the facility in control of the products?

- Conduct a timely investigation
- Create an appropriate corrective action plan
- Procedures to gain control of unsuitable products
- Determine appropriate disposition of all affected products
 - In-date and expired products
- Assess donor eligibility issues for future donations where applicable

Error Reporting Regulations

21 CFR 606.100(c) Standard Operating Procedures

- All records pertinent to the lot or unit maintained pursuant to these regulations shall be reviewed before the release or distribution of a lot or unit of final product. The review or portions of the review may be performed at appropriate periods during or after blood collecting, processing, compatibility testing and storing.
- A thorough investigation, including the conclusions and follow-up, of any unexplained discrepancy or the failure of a lot or unit to meet any of its specifications shall be made and recorded.

Error Reporting Regulations

21 CFR 211.192 Production Record Review

- 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.

How Are They Discovered?

- Record Review
- Staff Observation
- Internal Quality Audits
- External Audits
- Customer Complaints

Error Management

1. Discovery
2. Document
3. Immediate Correction
4. Investigation
5. Root Cause Analysis
6. Corrective Action
7. Effectiveness Evaluation

Is It Reportable?

Questions to consider:

- Are products distributed?
- Is it a donor safety issue only?
- Is SPP affected or *potentially* affected?
- Was a regulatory requirement violated?

Questions NOT to consider:

- Is the product in-date?
- Did I attempt retrieval or notify my consignee?

What Is Reported?

21 CFR 606.171

- You must report any event associated with manufacturing of both licensed and unlicensed blood or blood components that

Either:

- Represents a deviation from cGMPs, applicable regulations, applicable standards, or established specifications that may affect the safety, purity, or potency of that product, **or**
- Represents an unexpected or unforeseeable event that may affect the safety, purity, or potency of that product

And

- Occurs in your facility or a facility under contract with you

And

- Involves **distributed** blood or blood components

Distribution

*You must report any event associated with manufacturing of both licensed and unlicensed blood or blood components that involves **distributed** blood or blood components.*

21 CFR 606.3(k)

- The blood or blood component has left the control of the licensed manufacturer, unlicensed blood establishment, or transfusion service, **or**
- The licensed manufacturer has provided Source Plasma or any other blood component for use in the manufacture of a licensed biological product.

Who Must Report?

21 CFR 606.171(a)

- Licensed manufacturers of blood and blood components including Source Plasma
- Unlicensed, registered blood establishments
- Transfusion Services
- Facility that had control over the product when deviation from cGMP occurred is responsible for submitting report

Control

*Facility that had **control** over the product when deviation from cGMP occurred is responsible for submitting report.*

21 CFR 606.3(I)

Having responsibility for maintaining the continued safety, purity, and potency and for compliance with applicable product and establishment standards, and for compliance with cGMPs.

Contract Manufacturing

21 CFR 606.171(a)

- If you arrange for another person to perform a manufacturing, holding, or distribution step, while the product is in your control, that step is performed under your control. You must establish, maintain, and follow a procedure for receiving information from that person on all deviations, complaints, and adverse events concerning the affected product.

But We Don't Manufacture Products...

Manufacture per 21 CFR 607.3(d)

- The collection, preparation, processing, or compatibility testing by chemical, physical, biological, other procedures of any blood product that meets the definition of a drug, including manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process.

But We Aren't FDA Registered...

- Common misconception that only FDA registered facilities are required to report.
- Reporting is the law
- Error may be identified during an external inspection (AABB, CAP)

When To Report?

21 CFR 606.171(c)

- Report as soon as soon as possible
- You must report within 45 calendar days from the date that information is acquired by your facility of the deviation (date of discovery)
- The clock does NOT start when QA learns of the event

What Is Included In a BPD?

- Reporting establishment information
- Establishment information where deviation occurred
- BPD information
 - Internal tracking number
 - Dates of occurrence, discovery and report
 - Contributing factors/root cause
 - Corrective Action/Follow up
- Product information
 - DIN, dates of collection and distribution, disposition

How To Report?

21 CFR 606.171(e)

- You must report on Form FDA-3486.
- The completed form is sent to the Center for Biologics Evaluation and Research (CBER), either in paper or electronic format.
- FDA Industry Systems (FIS)

Non-Reportable Events

Deviations you are not required to report

- Affected products were not distributed
- It is determined prior to distribution that the SPP of the product was not affected
- The error is detected and corrected prior to distribution, (near miss)
- The event is strictly a donor safety issue
- Notification that the event was not reported to the FDA within 45 days

These events should be investigated as part of your error management system.

Examples by System



Donor Suitability

Reportable –

- Donor did not meet acceptance criteria
 - Hemoglobin/Hematocrit
 - Temperature
- Donor record incomplete or incorrect
- Deferral screening not done or incorrectly performed
- Donor gave history which warranted deferral – not deferred

Donor Suitability

Non-Reportable

- A recordkeeping deviation that would not affect the safety, purity, or potency of the product
- Donor did not meet suitability criteria related to donor safety only
 - Donor's weight and/or age
 - Donation intervals not met
 - More than 24 pheresis donations within 12 months.
 - These criteria do not affect product quality.

Collection

Reportable

- Arm preparation was not performed or was performed incorrectly
- Outdated bag or collection set was used in collection
- Outdated or incorrect anticoagulant was used in collection
- Defective device or collection bag was used for collection

Collection

Non-Reportable

- A recordkeeping deviation that would not affect the safety, purity, or potency of the product
- Donor has a reaction during the collection procedure.

Component Preparation

Reportable

- Component, such as Platelets or Fresh Frozen Plasma, was not prepared within the appropriate time frame after collection.
- Product was contaminated with bacteria, air or other contaminants during component preparation or processing, such as pooling.
- Component manufactured from a Whole Blood unit that did not meet specifications
- Incorrect filter was used for leukoreduction

Component Preparation

Non-Reportable

- A recordkeeping deviation that would not affect the safety, purity, or potency of the product

Testing

Reportable –

- Testing not performed in accordance with manufacturer's instruction
- Sample was tested in to compliance
- Expired reagents used for testing
- Testing was performed using a reagent or test kit in which QC was unacceptable or not documented

Testing

Non-Reportable

- A clerical error if there is other information to indicate that testing was performed appropriately
- Expired reagent used - if rare and no other reagent is available
- Duplicate concordant test results

Labeling

Reportable

- Product labeled with incorrect/missing ABO, Rh, antigen, antibody, product type, unit number, volume, weight
- Unit labeled with extended expiration date
- Additional information on autologous unit missing or incorrect
- Labeling indicating an incorrect recipient name or patient identifier

Labeling

Non-Reportable

- Unit labeled with incorrect collection date or facility identification
- Unit labeled with shortened expiration date
- HLA type incorrect or missing (*Only if the patient doesn't require an HLA matched unit*)
- Unlicensed product labeled with a license number
- Licensed product with an omitted license number
- Anticoagulant volume missing (*except WB*)

Quality Control & Distribution

Reportable

- Unsuitable unit distributed
- Failure to quarantine due to incorrect or incomplete testing
- SOP's for quality control or distribution not followed or inadequate
- Monthly QC Sampling Plan not met
- Unit not electronically shipped in the BECS
- Shipping/Storage requirements not met

Quality Control & Distribution

Non-Reportable

- Discrepancy between shipping invoice and the actual shipment
- Unit shipped to incorrect facility
- Unlicensed product labeled with a license number
- Disposition unknown for an acceptable unit
- Frozen product breaks during thawing and the product is discarded
- Unit returned to blood bank, determined to be unsuitable and discarded (e.g., out of temperature range)

BPD Summary Data

Table 2 - Blood and Source Plasma Establishments

Licensed Blood Establishments

Manufacturing System	FY16 (#)	FY16 (%)	FY17 (#)	FY17 (%)	FY18 (#)	FY18 (%)
DE-Post Donation Information	12,978	69.5%	12,792	71.2%	11,497	70.3%
Blood Collection	877	4.7%	918	5.1%	1,209	7.4%
Miscellaneous	1,370	7.3%	1,297	7.2%	1,028	6.3%
Quality Control & Distribution	1,215	6.5%	1,199	6.7%	949	5.8%
DE-Donor Screening	1,390	7.5%	860	4.8%	864	5.3%
Labeling	435	2.3%	471	2.6%	403	2.5%
LT-Routine Testing	193	1.0%	179	1.0%	201	1.2%
Component Preparation	169	0.9%	179	1.0%	164	1.0%
LT- Transfusion-Transmitted Infection Testing	13	0.1%	36	0.2%	21	0.1%
DE-Donor Deferral	24	0.1%	25	0.1%	15	0.1%
Total	18,664	100%	17,956	100%	16,351	100%

Example Scenarios – Is It Reportable?



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Scenario #1

A request was received for FFP and Platelets. Both products were prepared and made available. The doctor's orders were to transfuse both products, one after the other. The courier brought a release request for FFP, however the BB issued the platelets. The patient had been receiving both types of products over the past several days and the bedside nurse did not notice the wrong product was issued first and subsequently transfused the platelets.

FDA Reportable or Not?

FDA Reportable or Not?

- A. YES** —The pick-up slip was marked for FFP so the wrong product was issued.
- B. NO** —Both products were going to be given anyway so selecting either one to issue first still met the physician's specifications.
- C. NO** —There was nothing wrong with the product that was issued and transfused so it is not FDA reportable.

Scenario #2

An apheresis platelet product is irradiated. The product is modified in the BECS to reflect the irradiated product code and description. When the product is relabeled as an irradiated product, the product volume is electronically printed on the label, however, the anticoagulant volume from the original label is not transcribed on to the new label. The product is distributed to a consignee and the consignee notifies the blood center of the missing value since they are unable to enter it in to their LIS.

FDA Reportable or Not?

FDA Reportable or Not?

- A. YES** —SOPs for Irradiating and relabeling products were not followed and products were distributed.
- B. YES** —The label on the product was incomplete since the field for the anticoagulant volume was blank.
- C. NO** —The total product volume was on the label and apheresis Platelet products are not required to contain the anticoagulant volume.

Scenario #3

An insufficient number of products were tested for monthly product QC. Per the facility's sampling plan, 70 products were to be tested per month, but only 68 were tested.

FDA Reportable or Not?

FDA Reportable or Not?

- A. **NO** – there is no indication that safety, purity, potency was affected by shorting QC by 2 products
- B. **NO** – facilities are allowed a +/- 5 product variance in their sampling plans
- C. **YES** – the facility's product QC sampling plan was not met

Scenario #4

An autologous RBC product was issued with the appropriate autologous tie tag, but the ISBT product code used indicated the unit was from a volunteer donor. The blood center distributed the product to the hospital blood bank. The product was transfused to the correct autologous patient.

FDA Reportable or Not?

FDA Reportable or Not?

- A. NO** – the product was appropriately identified as autologous via the tie tag
- B. NO** – the product was issued to the appropriate patient
- C. YES** – the product was mislabeled as a volunteer donor with an incorrect product code

Scenario #5

A unit of A Pos RBCs is cross-matched and tagged patient John Smith. The unit is issued from the blood bank for John Smith. The nurse walks the unit to the wrong room and begins to transfuse the unit to Joanne Smith who is O Pos. The patient displays adverse reactions within minutes. The transfusion is stopped and a transfusion reaction investigation is ordered.

FDA Reportable or Not?

FDA Reportable or Not?

- A. YES** – A patient ID error was made and recipient safety was potentially affected at the time the transfusion was administered.
- B. NO** – If the unit is ultimately determined to be compatible with the recipient, FDA reporting is not required.
- C. NO** – The product was appropriately tested, issued and labeled for the intended recipient. It was the transfusing staff that was responsible for the error.

Scenario #6

A unit is cross-matched and then split in to two parts; A and B. Compatibility tags are printed and attached to each unit. Part A is issued and the bedside nurses notices that the attached form is not for Part A, but for Part B. The nurse returns the unit to the blood bank where it is discovered that the tags were switched. The error is corrected by manually changing the tags and placing them on the correct unit.

FDA Reportable or Not?

FDA Reportable or Not?

- A. YES** – The product left the control of the blood bank with the switched tag, even though it posed no patient safety risk.
- B. NO** – The bedside nurse caught the error and had it fixed so it was properly tagged at the time it was transfused.
- C. NO** – Both parts are from the same unit and were cross-matched for the same patient. There are no patient safety factors involved.

Scenario #7

A blood product was irradiated properly (as confirmed by the irradiation log and the irradiation indicator) however the product was not modified or relabeled as an “Irradiated” product. This was discovered at the bedside after issue, returned to the blood bank and corrected prior to transfusion.

FDA Reportable or Not?

FDA Reportable or Not?

- A. NO** – The irradiation indicator was properly applied to the product and clearly indicated it was irradiated, therefore it sufficiently served as a form of irradiation labeling.
- B. NO** – The labeling error was detected and corrected before it was transfused, therefore FDA reporting is not required.
- C. YES** – An error was made during the manufacture of the product, the labeling was incorrect and the product was issued.

Scenario #8

Expired panel cells were used as controls for anti-sera (anti-C, anti-E and anti-Jka). The expired cells are used to ensure the anti-sera will work as intended. The anti-sera was used to detect red cell antigens on donor RBCs. The unit is labeled based on this typing (C, E and Jka negative) and product is issued for transfusion. The test results of the expired cells were acceptable.

FDA Reportable or Not?

FDA Reportable or Not?

- A. **NO** – These were only used as controls not for actual testing.
- B. **YES** – Expired reagents used for QC testing is reportable if a unit was distributed based on these results.
- C. **NO** – Because all results were acceptable.

Scenario #9

A platelet unit expires at midnight. The unit is issued at 2030 and the transfusion started at 2045. At 00:20, the bedside nurse calls the transfusion service in a panic. She just realized that the product expired 20 minutes ago and they still have about 50 mL more to give before the transfusion is complete.

FDA Reportable or Not?

FDA Reportable or Not?

A. YES – If it's still being transfused longer than 4 hours after issue.

B. NO – It was issued and started before it expired.

C. YES – They transfused a product after it was expired.

Scenario #10

Two patient BBID's were on a unit of blood that was dispensed. Patient #1 was cross-matched but didn't get the unit and it was returned to inventory. The BBID wasn't removed and the unit was cross-matched for Patient #2. The double tag was not discovered until nursing was checking identification at patient bedside. The unit was returned to the blood bank upon discovery.

FDA Reportable or Not?

FDA Reportable or Not?

- A. NO** – The product was appropriately cross-matched to the second patient prior to release.
- B. NO** – Tie tag was labeled for the correct patient; it just had additional information
- C. YES** – The cross-match tag or tie tag was incorrect or had missing information; recipient identification incorrect or missing.

Scenario #11

Consignee notified the blood center an extra unit of Leukocyte Reduced Red Blood Cells was in the shipping container and was not listed on the shipping document. The component passed all QC, testing was normal and no deferrals on the donor. The component was in electronic inventory at the blood center and results were suitable for release.

FDA Reportable or Not?

FDA Reportable or Not?

A. NO – RBC product was suitable for release.

B. YES – Without electronic shipping, there is no evidence captured that visual inspection on the unit was performed prior to shipment.

C. NO – Product was acceptable for release, it just was not electronically dispositioned (shipped) in the BECS.

Scenario #12

An automated infectious disease testing analyzer has a failure (tray jam). The operator's manual states that calibration and temperature validation is required following problem resolution. The lab failed to perform the required calibration and validation following the failure repair. All analyzer internal and external run controls had acceptable results. Test results were released to the donor center and products were labeled and subsequently distributed.

FDA Reportable or Not?

FDA Reportable or Not?

A. NO – Although the required calibration and verification was not performed, the controls passed.

B. YES - Not performing prescribed maintenance/calibration/validation activities violates equipment regulations and the operator's manual instructions (which FDA states is a requirement to follow) and represents a condition that *may* affect safety or quality of products.

C. NO – A tray jam isn't really an instrument failure. There is no evidence that test results are compromised.

Who is responsible to report?

Who Reports?

A. Contracted Testing Laboratory – They made the error by not following the requirements of the operator's manual.

B. Donor Center – They distributed the products unaware of the error.

C. Both – Each location played a role in the impacted units being released.

Questions?

