

# Guidance for Industry

## Biological Product Deviation Reporting for Blood and Plasma Establishments

### *DRAFT GUIDANCE*

**This guidance document is being distributed for comment purposes only.**

Comments and suggestions regarding this draft document should be submitted by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

Additional copies of this draft guidance document are available from the Office of Communication, Training and Manufacturers Assistance, (HFM-40), 1401 Rockville Pike, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at <http://www.fda.gov/cber/guidelines.htm>.

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U.S. Department of Health and Human Services  
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## **GUIDANCE FOR INDUSTRY**

### **Biological Product Deviation Reporting For Blood and Plasma Establishments**

*This guidance document represents the Agency's current thinking on biological product deviation reporting for blood and plasma establishments. It does not create or confer any rights, privileges, or benefits on or for any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.*

#### **I. INTRODUCTION**

On November 7, 2000, the Food and Drug Administration (FDA) published a final rule to amend the requirements for reporting of errors and accidents in manufacturing of products. The rule amended the regulation at 21 CFR 600.14 and added a requirement at 21 CFR 606.171, applicable to all manufacturers of blood and blood components. The final rule

- expands the reporting requirement to include unlicensed registered blood establishments and transfusion services
- eliminates the terms "error" and "accident" and focuses on biological product deviations, which include deviations and unexpected events
- establishes a reporting time frame of 45 days from the date the deviation or unexpected event was discovered
- limits reporting to deviations or unexpected events that may affect distributed products

FDA published the rule for implementation within 180 days of the date of publication. This guidance document provides blood establishments with the Agency's current thinking related to the biological product deviation reporting requirements. For the purposes of this document, "blood establishment" includes licensed manufacturers of blood and blood components, including Source Plasma, unlicensed registered blood establishments, and transfusion services. The FDA uses mandatory language, such as shall, must, and require, when referring to statutory or regulatory requirements. The FDA uses non-mandatory language, such as should, can, and recommend, when referring to guidance. It is the responsibility of the manufacturer to read, understand, and follow the regulations.

#### **II. BACKGROUND**

Previously, in accordance with 21 CFR 600.14, only licensed blood and plasma establishments, and licensed manufacturers of other biological products, were required to promptly report errors and accidents in manufacturing that may affect the safety, purity, or potency of a product to FDA. On March 20, 1991, FDA issued a memorandum

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entitled, “Responsibilities of Blood Establishments Related to Errors & Accidents in the Manufacture of Blood & Blood Components” requesting voluntary reporting from unlicensed registered blood establishments and transfusion services. In the Federal Register of September 23, 1997 (62 FR 49642), FDA published a proposed rule to amend the reporting requirements for manufacturers of blood and blood components as described above. In response to some of the comments received, FDA is providing this guidance document to clarify the reporting requirements for blood establishments.

The new regulation at 21 CFR 606.171 requires reporting of any event associated with the manufacturing, to include testing, processing, packing, labeling, or storage, or with the holding or distribution of blood or a blood component, in which the safety, purity, or potency of a distributed product may be affected. A blood establishment is required to report to the Center for Biologics Evaluation and Research (CBER), Office of Compliance and Biologics Quality (OCBQ) as soon as possible, but not to exceed 45 calendar days from the date of discovery of information reasonably suggesting a reportable event has occurred. To facilitate reporting, FDA has developed a standardized reporting format that blood establishments may submit electronically or in paper form, by mail.

The new regulation does not change any of the requirements in 21 CFR Part 606 or Part 211 for conducting investigations of manufacturing deviations or product deficiencies. Those regulations require an establishment to thoroughly investigate unexplained discrepancies and failures to meet specifications, and to maintain complaint records, including records of investigations and follow-up. Procedures should include provisions for

- a timely investigation
- a corrective action plan, both short term and long term, to prevent recurrence
- procedures to gain control of unsuitable products in a timely manner
- appropriate disposition of all affected products (in-date and expired)
- for deviations and discrepancies associated with donor suitability, an assessment of the donor’s suitability to serve as a donor in the future.

For additional information refer to the “Guideline for Quality Assurance in Blood Establishments.”

### **III. GUIDANCE**

#### **A. WHO MUST REPORT? [Section 606.171 (a)]**

Under 21 CFR 606.171, the manufacturer who had **control** over the product when a deviation or unexpected event (“event”) occurred must submit a biological product deviation report. This reporting requirement applies to licensed manufacturers of blood and blood components, including Source Plasma, to unlicensed registered blood establishments, and to transfusion services.

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“Control” is defined in section 606.3(l) as having responsibility for maintaining the continued safety, purity and potency of the product and for compliance with applicable product and establishment standards and compliance with current good manufacturing practices.

There may be firms, such as plasma fractionators, that collect Source Plasma or other blood components to be used as source material for further manufacture into a finished product. Deviations and unexpected events that occur during the manufacture of such source material must be reported under 21 CFR 606.171. Deviations and unexpected events that occur during the manufacture of a finished product that is licensed (e.g., Immune Globulin Intravenous, Human) must be reported under 21 CFR 600.14. A separate draft guidance document for reporting biological product deviations that occur in the manufacture of biological products other than blood and blood components, entitled “Biological Product Deviation Reporting for Licensed Manufacturers of Biological Products Other than Blood and Blood Components” is available from the Internet at <http://www.fda.gov/cber/guidelines.htm>.

Sometimes, a blood establishment establishes a contract with another entity to perform some or all of the manufacture of a product. Some common manufacturing steps performed under contract include testing (e.g., viral marker or compatibility), irradiation, blood collection, storage and distribution. If you contract out any manufacturing step, for the purposes of 21 CFR 606.171 and as described in this guidance document, that step is performed under your control. Under 21 CFR 606.171(a), you must establish a system for receiving information from that contract manufacturing facility on all deviations, complaints, and adverse events.

If you are a *Contract Manufacturer* (i.e., perform a step in manufacturing for another establishment under contract), you must conduct such manufacturing in accordance with all applicable regulations but you are not considered to have control over the product, for the purposes of submitting biological product deviation reports to FDA.

**Examples:**

**1. BIOLOGICAL PRODUCT DEVIATION**

A blood bank contracts with a test laboratory to perform viral marker testing. The test laboratory did not perform the testing in accordance with the test kit manufacturer’s instructions, which may affect the safety, purity, or potency of the product.

**REPORTING**

The test laboratory must perform an investigation under 21 CFR 606.100(c), 211.192, and 211.198. The test laboratory should provide the blood bank with details of the deviation in viral marker testing. The test laboratory is NOT required to report to FDA.

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The blood bank must establish a procedure for receiving information from the test laboratory about deviations concerning the viral testing. The blood bank must report a biological product deviation to FDA if it distributed the improperly tested product. The blood bank should assure that the test laboratory performed an adequate investigation.

**2. BIOLOGICAL PRODUCT DEVIATION**

A blood bank contracted with another establishment (irradiator) to perform irradiation of blood products. The blood bank sent a product to the irradiator, which returned the product to the blood bank after irradiation. The irradiator notified the blood bank that all irradiation procedures were not followed (i.e., established specifications were not met), which may affect the safety, purity, or potency of the product.

**REPORTING**

The irradiator must perform an investigation under 21 CFR 606.100(c), 211.192, and 211.198. The irradiator should provide the blood bank with details of the deviation in the irradiation process. The irradiator is NOT required to report to FDA.

The blood bank must establish a procedure for receiving information from the irradiator about deviations concerning the irradiation process. The blood bank must report a biological product deviation to FDA if it distributed the improperly irradiated product. The blood bank should assure that the irradiator performed an appropriate investigation.

**3. BIOLOGICAL PRODUCT DEVIATION**

A blood bank distributed a blood product to another establishment (irradiator), which subsequently irradiated it. The irradiator did not follow all irradiation procedures (i.e., established specifications were not met), which may affect the safety, purity, or potency of the product.

**REPORTING**

The irradiator must perform an investigation under 21 CFR 606.100(c), 211.192, and 211.198. The irradiator must report a biological product deviation to FDA if it distributed the improperly irradiated product. The blood bank is NOT required to report to FDA or perform an investigation because the product was not in its control at the time the event occurred, i.e., it was not irradiated under a contract manufacturing agreement.

**4. BIOLOGICAL PRODUCT DEVIATION**

A transfusion service received a unit of Platelets from a blood center. At the time of receipt, the transfusion service discovered that the unit was labeled with an expiration date of more than the required 5 days (i.e., improperly extended), which may affect the safety, purity, or potency of the product. The transfusion service notified the blood center.

**REPORTING**

The blood center must perform an investigation of the deviation in labeling under 21 CFR 606.100(c), 211.192, and 211.198. The blood center must report a biological product deviation to FDA.

The transfusion service is NOT required to report to FDA unless it further distributed the unit without appropriately correcting the label.

**5. BIOLOGICAL PRODUCT DEVIATION**

A transfusion service received 10 units of Platelets and subsequently pooled them into one unit. The transfusion service improperly labeled the pooled unit with an incorrectly extended expiration date, which may affect the safety, purity, or potency of the product.

**REPORTING**

The transfusion service must investigate the deviation in labeling under 21 CFR 606.100(c), 211.192, and 211.198. The transfusion service must report a biological product deviation if it distributed (i.e., released for transfusion) the mislabeled product.

**6. BIOLOGICAL PRODUCT DEVIATION**

A transfusion service received a unit of Red Blood Cells from a blood center that had an expiration date incorrectly extended. The transfusion service should have recognized that the expiration was extended beyond any date appropriate for Red Blood Cells. The transfusion service crossmatched the unit for a patient and distributed it to the surgical floor for transfusion. When the empty bag was returned to the transfusion service, it was discovered that the unit was labeled with an extended expiration date, which may affect the safety, purity, or potency of the product.

**REPORTING**

Under 21 CFR 606.100(c), 211.192, and 211.198, the transfusion service is required to perform an investigation of the inappropriate release of a unit with an incorrectly extended expiration date because the transfusion service failed to recognize the extended expiration date at the time of receipt or compatibility testing. The transfusion service must report a biological product deviation to FDA and notify the blood center of the incorrect labeling.

The blood center must perform an investigation of the deviation in labeling under 21 CFR 606.100(c), 211.192, and 211.198. The blood center must also report a biological product deviation to FDA.

7. **BIOLOGICAL PRODUCT DEVIATION**

A source plasma center collected and tested a unit, and shipped it to a fractionator, a licensed manufacturer. The plasma center then discovered that the testing was incorrectly performed for anti-HIV. When tested correctly, the unit actually tested repeatedly reactive for anti-HIV. The plasma center should not have distributed this unit, because the safety, purity, or potency of the product may be affected.

**REPORTING**

The plasma center must perform an investigation of the improper testing and distribution of the unit under 21 CFR 606.100(c), 211.192, and 211.198. The plasma center is required to report a biological product deviation to FDA under 606.171. The plasma center should also notify the fractionator.

The fractionator is required to report a biological product deviation under 21 CFR 600.14, if it used the improperly tested plasma in the manufacture of a licensed biological product and distributed the final product because the safety, purity, or potency of the final product may be affected. Additional guidance for fractionators is provided in the document, "Biological Product Deviation Reporting for Licensed Manufacturers of Biological Products Other than Blood and Blood Components."

B. **WHAT DO I REPORT? [Section 606.171(b)]**

You must report any event associated with the manufacturing, to include testing, processing, packing, labeling, or storage, or with the holding or distribution, of both licensed and unlicensed blood or blood components, including Source Plasma, if that event meets all the following criteria:

- (1) Either;
  - (i) Represents a deviation from current good manufacturing practices (cGMP), applicable regulations, applicable standards, or established specifications that may affect the safety, purity, or potency of that product; or
  - (ii) Represents an unexpected or unforeseeable event that may affect the safety, purity, or potency of that product; and
- (2) Occurs in your facility or a facility under contract to you; and
- (3) Involves distributed blood or blood components.

You must establish a procedure to determine when a biological product deviation must be reported to FDA. The procedure should include a process to assess whether or not an event is reportable. The decision to report should not be based on an investigation into whether the event affected the safety, purity, or potency, but whether the event had the **potential** to affect the safety, purity, or potency of a product. The procedure should not

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consist of a list of examples of reportable and non-reportable events alone. Examples may be included in the procedure for reference.

In general, a biological product deviation report is **not** required:

1. When no affected products are distributed, regardless of the deviation or unexpected event.
2. When it is determined prior to distribution that the safety, purity, or potency of a product is not affected.
3. When the deviation or unexpected event is related to donor safety only and did not have the potential to affect the safety, purity, or potency of the product.
4. Simply to report that you were late in reporting the deviation or unexpected event to FDA.
5. When a deviation or unexpected event is detected and appropriately corrected prior to distribution.
6. When there is a change in a procedure, which does not have the potential to affect the safety, purity, or potency of a product, that requires prior CBER approval or notification and products are released before approval is received or before the notification is made.

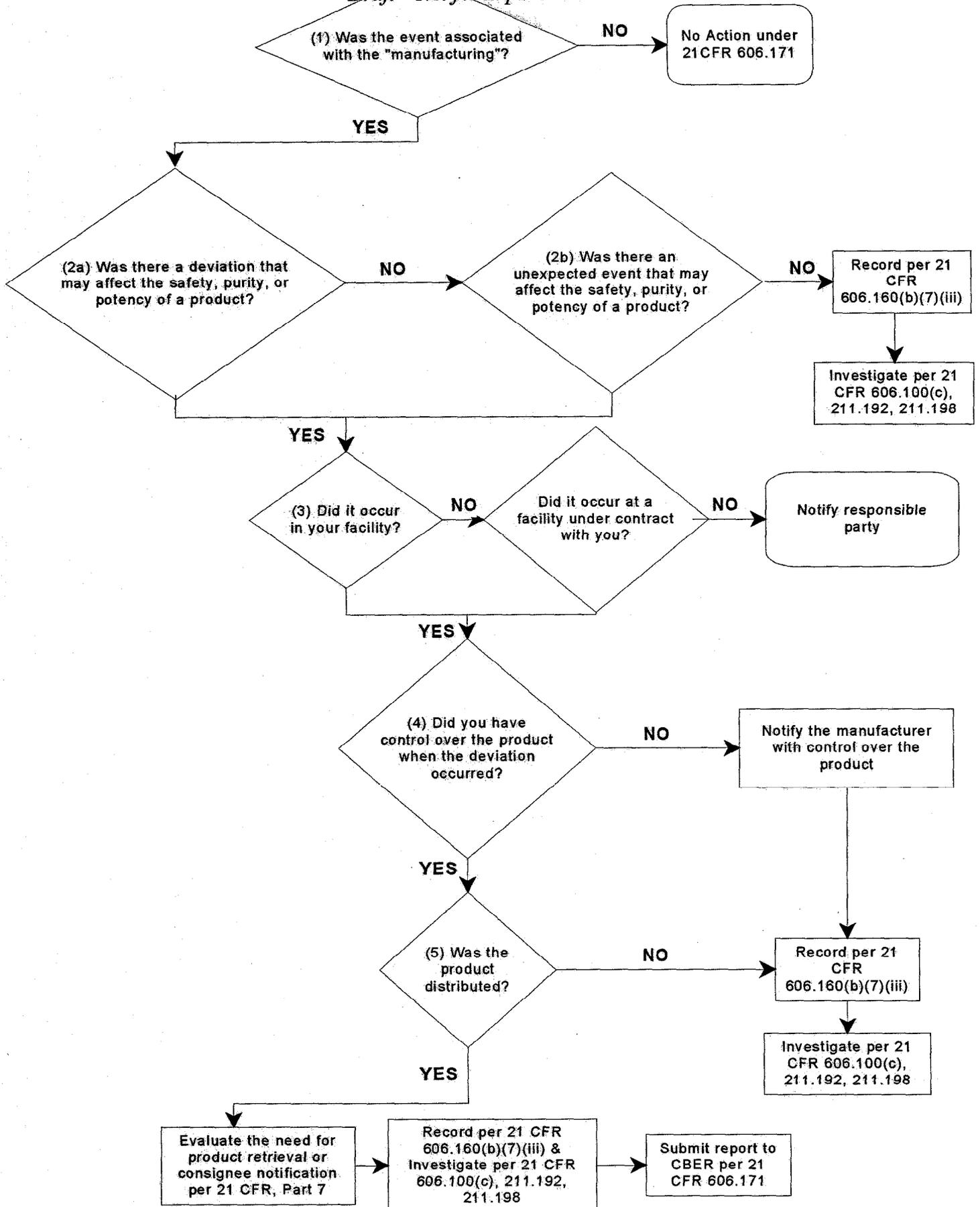
It is important to note that while the above examples would not be reportable under 21 CFR 606.171, the events may constitute deviations from the regulations, which will be assessed by FDA in the context of overall operations.

**Biological Product Deviation Reporting Flow Chart**

The following flow chart may be used to aid in determining if you are required to report an event to FDA.

# BIOLOGICAL PRODUCT DEVIATION REPORTING FLOW CHART

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The following questions correspond to the flow chart:

**(1) Was the event associated with the “manufacturing” as it is broadly described in the regulation?**

In 21 CFR 606.171, manufacturing is described to include testing, processing, packing, labeling, or storage, and the holding or distribution of blood or blood components. These activities include the collection, preparation, processing or compatibility testing of any blood product.

If the deviation or unexpected event was associated with manufacturing, you should determine whether the event may affect the safety, purity, or potency of a product. If it was not associated with the manufacturing, you are not required to report to FDA according to 21 CFR 606.171.

Deviations and unexpected events that occur after release or distribution of products from the blood establishment, including those related to the administration of blood or blood components, are not reportable as biological product deviations according to 21 CFR 606.171.

**Examples**

1. A *Transfusion Service* is NOT required to report a biological product deviation if the event occurs during transfusion or administration procedures, after the blood product has left the control of the transfusion service. For example, a report is not required

a) if the transfusion service (i.e., blood bank) released a unit for transfusion to the nursing floor, operating room, emergency room, etc., and the unit was not held at the appropriate temperature outside of the blood bank prior to transfusion. However, the transfusion service is required to report if the unit was returned and the transfusion service determined it to be unsuitable, but reissued the unit.

b) if the hospital staff, outside of the blood bank, transfused the wrong patient or transfused a patient with the wrong unit, provided the unit was labeled appropriately. If a complication of a transfusion was confirmed to be fatal, the facility that performed the compatibility testing must submit a **fatality report** to FDA in accordance with 21 CFR 606.170 (b).

c) if the transfusion service issued a filter with the unit and the hospital staff did not use the filter at the bedside.

2. A *Blood Bank* is NOT required to report if the event is not associated with its manufacturing process. For example the blood bank is not required to submit a report:

- a) if the blood bank shipped a unit to another facility and the receiving facility stored the unit at the incorrect temperature before processing. If the receiving facility further distributed the unit, the receiving facility must submit a report.
- b) if the blood bank received an unacceptable unit from another blood establishment and returned or discarded the unit. The blood establishment that distributed the unacceptable unit must submit a report.

**(2a) Was there a deviation that may affect the safety, purity, or potency of a product?**

A deviation that may affect the safety, purity, or potency of a product could include any change in the manufacturing process that would prevent a product from meeting all current good manufacturing practice (cGMP) requirements, applicable standards and established specifications. CGMP and applicable regulations for blood and blood components are currently found in 21 CFR Parts 210, 211, 600, 606, 610, and 640. Established specifications refer to defined product or process parameters. Generally these are incorporated into standard operating procedures to help ensure the safety, purity and potency of products. They may describe the specifics of a product, such as the hematocrit level, or the specifics of a process, such as the temperature range for thawing a frozen component.

**(2b) Was there an unexpected or unforeseeable event that may affect the safety, purity, or potency of a product?**

An unexpected or unforeseeable event is one in which, despite the fact that a blood establishment followed all required procedures, something occurred that may affect the safety, purity, or potency of a product. This may be due to information that the blood establishment did not have at the time of manufacturing. Examples of unexpected or unforeseeable events in which the safety, purity, or potency may be affected include the following:

- (i) **Post Donation Information** – A donor donated blood on one occasion. The blood establishment followed all donor screening and deferral procedures, and determined that the donor was suitable. At a second donation, the donor disclosed additional information that would have resulted in deferral had the donor disclosed it at the earlier donation, such as information that the donor received a tattoo within 12 months of the first donation.

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(ii) After the product is distributed, it's discovered that the blood establishment performed compatibility testing using a patient sample that was collected from the wrong patient or labeled with incorrect patient information.

(iii) After the product is distributed, the blood establishment is informed by a manufacturer of materials used in the collection or processing of blood and blood components, such as reagents, soft goods, software, or collection device, that the manufacturer's product did not meet all requirements or specifications, and the blood establishment could not have detected the deviation during routine incoming material qualification procedures.

If an event occurred, but could not affect the safety, purity or potency of a product, it must be recorded in accordance with 21 CFR 606.160(b)(7)(iii) and investigated in accordance with 21 CFR 606.100(c), 211.192 and 211.198, but no biological product deviation report to FDA is required.

*If you discover a deviation or unexpected event after distribution of any affected products and the safety, purity, or potency of the product may have been affected at the time of distribution, you are required to report the event. You must report the event under 21 CFR 606.171 even if you determine, through investigation, that the safety, purity or potency of the product was not affected.*

For example, if you distributed an untested unit, you must report that to FDA, even if you subsequently tested the unit and found it to be negative.

*If you discover a deviation or unexpected event prior to distribution of any affected products and determine that the safety, purity, or potency of the product was not affected, you do not need to report under 21 CFR 606.171.*

For example, if you discovered a deviation in testing prior to the distribution of a unit and you appropriately retested the unit and found it to be negative, you are not required to report to FDA under 21 CFR 606.171.

**(3) Did it occur in your facility or at another facility under contract with you?**

A report is required if the event occurs within your facility or a facility under contract with you, such as a testing laboratory. You must report events that occur at the contractor and, therefore, you must establish, maintain, and follow a procedure for receiving information from the contract facility on all deviations, complaints, and adverse events concerning the affected product.

If you are a *contract manufacturer*, such as a testing laboratory, and an event occurs within your facility, you should notify the manufacturer with control over the product. You are not responsible for reporting the event to FDA.

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If you detect an event that occurred at another facility not under contract with you, you should contact that facility, which would be responsible for reporting to FDA, if appropriate. For example, if you receive a unit of Red Blood Cells shipped without ice you should notify the supplier. You are not required to report to FDA unless you further distributed the unacceptable unit.

**(4) Did you have control over the product when the deviation occurred?**

You have control over the product if you have overall responsibility for

- maintaining the continued safety, purity, and potency of the product
- compliance with applicable product and establishment standards, and
- compliance with current good manufacturing practices.

You are responsible for reporting if you have control over the product and distributed the affected product.

You have control over the product if you contract with another entity to perform all or some of the manufacture of a product. Under 21 CFR 606.171(a), you must establish a system for receiving information from the contract manufacturing facility on all deviations, complaints and adverse events. The *contract manufacturer* is responsible for documenting the event in accordance with 21 CFR 606.160(b)(7)(iii) and investigating in accordance with 21 CFR 606.100(c), 211.192 and 211.198. The contract manufacturer is not responsible for reporting to FDA.

**(5) Was the product distributed?**

Distributed is defined in section 606.3(k) as

- (1) the blood or blood component has left the control of the licensed manufacturer, unlicensed registered blood establishment, or transfusion service; or
- (2) the licensed manufacturer has provided Source Plasma or any other blood component for use in the manufacture of a licensed biological product.

In the case of a licensed blood establishment, the unit is considered distributed when it has been shipped to another facility or broker that is not part of the license. The unit is **not** considered distributed if it is shipped from one location to another and both locations are under the same license.

In the case of an unlicensed registered blood establishment or transfusion service, the unit is considered distributed when it has been released or issued to staff outside of the blood bank for transfusion or is shipped to another facility or broker.

In the case of a Source Plasma Center, the unit is considered distributed when it has been released or shipped for further processing. Distribution includes shipment to a plasma broker. Distribution does not include shipment to an off-site storage facility that is under the Source Plasma Center's control.

## Examples

- (i) If a blood establishment labeled a unit with an extended expiration date and shipped it to a hospital, the blood establishment must report to FDA.
- (ii) If a hospital blood bank received 10 units of platelets from a blood center, pooled the platelets, mislabeled the final pooled product with an incorrectly extended expiration date, and released or issued the product to the nursing staff for transfusion, the hospital blood bank must report to FDA. However, if the extended expiration date is detected and corrected prior to distribution of the product, the blood bank must document and investigate the deviation but is not required to submit a biological product deviation report.

If the product was distributed, you should also assess the need for product retrieval or consignee notification in accordance with 21 CFR Part 7. The event must be documented in accordance with 21 CFR 606.160(b)(7)(iii) and investigated in accordance with 21 CFR 606.100(c), 211.192 and 211.198, regardless of whether or not the product was distributed.

### C. WHEN DO I REPORT? [Section 606.171 (c)]

You must report a biological product deviation as soon as possible, but at a date not to exceed 45 calendar days from the date that you acquire information reasonably suggesting that a reportable event has occurred. You acquire such information when any employee of your facility, not just those involved in quality assurance or quality control activities, learns about the event. As soon as you acquire information, you should make an assessment of whether the event had the potential to affect the safety, purity, and potency of products and determine the status of the products (whether they were distributed or need to be quarantined).

If you contract with a facility to perform a manufacturing step and a deviation or unexpected event occurred at the contractor, the time period for reporting will start when your contractor learns about the deviation or unexpected event.

### D. HOW DO I REPORT? [Sections 606.171 (d) and (e)]

You must use FDA Form-3486 to report biological product deviations. This report may be submitted electronically through CBER's web site at <http://www.fda.gov/cber/biodev/biodev.htm>, or by mail to:

Director, Office of Compliance and Biologics Quality (HFM-600)  
Center for Biologics Evaluation and Research  
1401 Rockville Pike, Suite 200N  
Rockville, Maryland 20852-1448

If the event occurred at your contract manufacturer, you should include in the Biological Product Deviation Report, details reported to you by the contract manufacturer regarding the event.

#### **IV. EXAMPLES OF REPORTABLE AND NON-REPORTABLE EVENTS BY SYSTEM**

FDA categorizes biological product deviations according to the system where the breakdown or failure occurred that resulted in the distribution of an unsuitable unit. It is important for you to know where the failure occurred that allowed the product to continue through the process of manufacturing and distribution, so that you can take the appropriate follow-up action. An event may be the result of a failure within a variety of systems, depending on the circumstances.

- *A donor suitability deviation or unexpected event* occurs in the donor suitability process (for example, donor screening, donor deferral procedures and receipt of post donation information) (See Section IV. A).
- *A collection deviation or unexpected event* occurs during the collection process (See Section IV. B).
- *A component preparation deviation or unexpected event* occurs during the component preparation process (See Section IV. C).
- *A testing deviation or unexpected event* occurs during the testing process and includes sample deviations and unexpected events (See Section IV. D).
- *A labeling deviation or unexpected event* occurs during the labeling process, which includes identifying the information to include on the label, printing the label, and applying the label to the product (See Section IV. E).
- *A quality control and distribution deviation or unexpected event* involves a failure in either the quality control (QC) or distribution systems. This category includes the distribution of an unsuitable product and the distribution of product not in accordance with SOP's (See Section IV. F).

#### **Retrieval, Consignee Notification and Lookback**

You must implement and follow procedures for the retrieval of products and consignee notification and maintain adequate records for such retrieval or notification. In addition, you must implement and follow procedures for "Lookback" in accordance with 21 CFR 606.100(b)(19), 610.46 and 610.47. You are not required to file a biological product deviation report simply because you fail to follow your own internal procedures for retrieval, notification or lookback (e.g., you do not have to file a report if you did not notify consignees within the time frame prescribed in your procedures). This type of deviation is not required to be reported because the safety, purity, or potency of the

product was not affected by the failure to follow retrieval, notification, or lookback procedures. However, you must file a report if the underlying reason for the retrieval, notification, or lookback meets the reporting criteria found in Section III.B. In that case, the report must describe the deviation or unexpected event that may have affected the safety, purity, or potency of the product.

The following examples of deviations or unexpected events are not all-inclusive and do not represent all variations that may occur. The examples include deviations from the regulations, standard operating procedures (SOPs) and established specifications. Not all of these examples will necessarily apply to you, but will depend on your manufacturing operations and procedures. All deviations and unexpected events must be investigated in accordance with 21 CFR 606.100(c), 211.192, and 211.198, regardless of whether or not they are reportable.

#### A. DONOR SUITABILITY

Over the past several years, donor suitability issues have represented the largest percentage of error and accident reports. This category includes post donation information, donor screening, and donor deferral.

##### (1) Post Donation Information

The majority of reports related to donor suitability involve post donation information. FDA issued a Memorandum to All Blood Establishments entitled, "Guidance Regarding Post Donation Information Reports," on December 10, 1993 which describes the process for handling post donation information. This guidance does not supercede the memorandum, but provides additional information regarding reporting post donation information.

Post donation information includes information that is provided by a donor or other reliable source subsequent to a donation. Post donation information can be provided by the donor or a third party, and is often reported at a subsequent donation. Post donation information is reportable as a biological product deviation if the donor should have been deferred had the information been known at the time of donation and the safety, purity, or potency of the product could be affected. It is also reportable if the medical evaluation reasonably suggests that the safety, purity, or potency of the product could be affected, or the information is insufficient to conclude that the safety, purity, or potency of the product is not affected, such as when a donor subsequently instructs an establishment not to use the donor's blood, without providing a reason.

Post donation information also includes information that a blood center obtains when it adds new donor history questions. In response to a new question, donors may provide information that they did not provide at an earlier donation. If the additional information may affect the safety, purity, or potency of the product, you must file a report.

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Examples of Post Donation Information include, but are not limited to:

- Donor received a tattoo, ear or body piercing, accidental needlestick, or transfusion less than 12 months prior to donation and did not report this at the time of donation
- Donor traveled to an area considered endemic for malaria less than 1 year prior to donation and did not report this at the time of donation
- Donor spent 6 months or more in the United Kingdom from 1980 through 1996

In some cases blood establishments cannot control post donation information, but they are responsible for the safety, purity, and potency of the product and for compliance with applicable standards and current good manufacturing practices. For example, a donor may call after donating to report a post donation illness, or information obtained post donation about exposure to a disease or a sex partner at high risk. This represents approximately 30% of the post donation information reports submitted to FDA. The remaining 70% of the reports involve situations in which the donor has knowledge of a behavior or risk factor prior to donation that would cause the donor to be unsuitable, but the donor fails to report this at the time of donation. At some point after donation, these donors provide information that results in deferral. You must have a process for evaluating all deviations and unexpected events under 21 CFR 606.100(c), including post donation information reports, whether reportable to FDA as a biological product deviation or not. Appropriate follow-up of post donation information reports may include, but is not limited to

- Evaluation of trends to determine the type of post donation information that is provided by your donors
- Periodic review as part of your audit process, which may include
  - Review of donor records to determine if information was provided at a previous donation that was not fully investigated
  - Review of the donor history questions to assure that they are understood by your donor population
  - Evaluation of donor screeners to assure they are asking the questions appropriately and they understand the purpose of asking the questions and how to interpret the donor's response
  - Interviewing the donor to determine why the donor provided additional information at one donation and not at the previous donations

Other similar situations that would be reportable as an unforeseen or unexpected event that may affect the safety, purity, or potency of previously distributed products include:

- Donor implicated in transfusion associated disease, unless donor is subsequently ruled out as the cause
- Donor tested negative and products were distributed, the donor returns and subsequently tested positive for any viral marker

Post Donation Information

**DO NOT REPORT:**

- Donor provides information of cold or flu symptoms to include any of the following symptoms: general malaise, cough, headache, fatigue, congestion, nausea, vomiting, chills, or runny nose that developed after the donation. The safety, purity, or potency is generally not likely affected by post donation cold or flu symptoms provided the donor screening process is adequate to detect and defer a donor who presents with any of these symptoms at the time of donation.
- Donor provides information that she was pregnant at the time of donation. This is a donor safety issue and not one that affects the quality of the product.

**(2) Donor Screening and Deferral**

Donor screening and deferral deviations and unexpected events include those relating to the determination of the eligibility of a donor. This includes the interview process, the medical evaluation process, the blood donor record documentation, and deferral procedures and records.

**(i) Interview process**

A biological product deviation report is required when either of the following events occurs and products are **distributed**:

- Donor provides information which warrants deferral and the donor is accepted
- Donor provides partial information which is not resolved by follow-up questioning and the donor is accepted

**(ii) Medical evaluation**

A biological product deviation report is required when any of the following events occur and products are **distributed**:

- Donor's hemoglobin or hematocrit is unacceptable
- Donor's temperature is unacceptable
- Plateletpheresis donor had an unacceptable platelet count and there is no documented platelet count for the unit

**(iii) Donor record documentation**

A biological product deviation report is required when any of the following events occur and products are **distributed**:

- No documentation of hemoglobin, hematocrit, donor's temperature, arm inspection
- Answers to the donor history questions, including high risk questions, are missing or incomplete, except those only affecting donor safety
- SOP's for documentation are not followed or not adequate, for example:
  - Both confidential unit exclusion stickers applied to unit
  - Confidential unit exclusion stickers applied by person other than donor

(iv) *Deferral procedures*

A biological product deviation report is required when any of the following events occur and products are **distributed**:

- Donor incorrectly omitted from the deferral list, which allowed the donor to subsequently donate
- Deferral list contains inaccurate information, such as identified as temporary deferral instead of permanent deferral or deferred for the incorrect reason, which allowed the donor to subsequently donate
- Donor not reentered properly after testing positive for a viral marker test
- Incorrect donor identification information used to check the deferral list (regardless of whether the donor was previously deferred). A report is required even if the donor provides discrepant identification information, such as different names on two donations – J. Michael Smith and James M. Smith.
- The deferral list was not checked (regardless of whether the donor was previously deferred)

Donor Screening and Deferral

**DO NOT REPORT:**

- Autologous donor did not meet the suitability criteria and the medical director has authorized the acceptance of the donor, provided the unit is labeled appropriately and not crossed over for allogeneic use.
- Donor suitability criteria, related to donor safety only, are not met, such as donor's weight, age, donating 56 days of last donation, or more than 24 pheresis donations within 12 months. These criteria do not affect product quality.
- Plateletpheresis donor had an unacceptable platelet count, but the platelet count for the unit is acceptable
- Blood donor record was not reviewed appropriately prior to distribution of the product, e.g., second or supervisory review not performed, but information was determined to be acceptable
- Deferral list was not checked or incorrect information was used in checking the deferral list and it is determined **prior to distribution** of products from that donation that the donor was not previously deferred.
- Donor inappropriately accepted and additional information obtained from the donor, **prior to distribution** of any products, demonstrates that the donor is acceptable
- Donor was deferred and products were handled appropriately, but the donor was not placed on the deferral list and did not have subsequent donations, therefore there were no products affected

## **B. COLLECTION**

Collection deviations and unexpected events include those that occur during the collection process.

A biological product deviation report is required when any of the following events occur and products are **distributed**:

- Unit identified as contaminated or potentially contaminated with bacteria or air
- Arm preparation not performed or performed incorrectly
- Outdated bag or collection set used in collection
- Outdated anticoagulant was used
- Defective device was used for collection
- Donor overbled and the unit was distributed as Whole Blood (product may be affected if there was an inadequate volume of anticoagulant)
- SOP's for collection not followed or not adequate, for example:
  - Collection time extended
  - Collection time discrepant
  - Collection time not documented
  - Collection status (e.g., satisfactory) not documented

### Collection

#### **DO NOT REPORT:**

- Phlebotomist's signature was missing from the donor record
- Donor has a non-fatal reaction during the collection procedure. If the donor has a fatal reaction as a result of a complication of blood collection, it is not reportable as a biological product deviation, but the collection facility must report to CBER in accordance with the requirements for reporting fatalities [21 CFR 606.170(b)].

## **C. COMPONENT PREPARATION**

Component preparation deviations and unexpected events include those that occur during the preparation or processing of a unit.

A biological product deviation report is required when any of the following events occur and products are **distributed**:

- Components, such as Platelets or Fresh Frozen Plasma were not prepared within appropriate time frame after collection
- Product became contaminated with bacteria, air or other contaminants during component preparation or processing, such as pooling

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- SOP's for component preparation not followed or not adequate, for example
  - Component not manufactured according to established specifications which may affect the safety, purity, or potency for that particular product, such as:
    - ◆ Platelets prepared from a unit collected from a donor who took aspirin or other drugs that affects platelets
    - ◆ Freezing time requirements not met for Fresh Frozen Plasma or Cryoprecipitate
    - ◆ Resting time for platelets not met
  - Components manufactured from an unsuitable Whole Blood unit, such as
    - ◆ Overweight or underweight Whole Blood unit
    - ◆ Whole Blood unit collected or stored at unacceptable temperature
    - ◆ Collection time of a Whole Blood unit was extended or not documented or collection was considered difficult or slow
  - Specific processing procedures, such as leukoreduction or irradiation, not followed according to cGMPs, standards or specifications which may affect the safety, purity, or potency, for example
    - ◆ Incorrect filter used for leukoreduction
    - ◆ Unit not leukoreduced within the appropriate time frame
    - ◆ Incorrect dosage used for irradiation
    - ◆ Procedure for washing/deglycerolization not followed

Component Preparation

**DO NOT REPORT:**

- A recordkeeping deviation such as the signature of the person preparing the unit was missing, or other documentation deviations that would not affect the safety, purity, or potency of the product.

**D. TESTING**

Testing deviations and unexpected events include those that occur during the testing process. Testing includes all those tests used to assure the safety, purity, and potency of a product, whether required by specific regulations or required by an establishment's standard operating procedure. Use of an unsuitable or inappropriate sample may also be a testing deviation or unexpected event.

A biological product deviation report is required when any of the following events occur and products are **distributed**:

- Testing not performed in accordance with manufacturer's instructions, such as
  - Incorrect incubation time or temperature
  - Incorrect reagents used/using reagents from two different lots
  - Incorrect addition of reagents (incorrect sequence, volume or concentration)
- Initial reactive not repeated in duplicate (viral marker testing)
- Testing into compliance (repeat testing until negative result obtained)

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- Inappropriate invalidation of assay
- Unsuitable sample used for testing, such as
  - Sample improperly stored
  - Sample diluted (e.g., saline dilution of samples collected after an apheresis procedure)
  - Sample is not identified appropriately to relate back to donor or patient being tested

For *transfusion services*, this also includes:

- Samples used for ABO/Rh, and compatibility testing that were collected outside the blood bank that were either mislabeled or collected from the wrong patient
- Mistyping or misinterpretation of patient samples if the sample was used in crossmatching a unit that was distributed

Testing

**DO NOT REPORT:**

- A failure to make one testing record if there are other testing records to indicate that testing was performed appropriately
- Appropriately invalidated assay and samples were retested and tested negative

**E. LABELING**

Labeling deviations and unexpected events include those that occur during the labeling process. Labeling deviations include incorrect, missing or misleading information on any labeling pertaining to the unit, including the unit label, tie tags, the circular of information, and the labeling accompanying the unit that identifies the patient for whom it has been crossmatched.

A biological product deviation report is required when any of the following events occur and products are **distributed**:

- Unit labeled with an incorrect ABO or Rh type, antigen type, antibody, product type, donor number, anticoagulant, volume or weight
- Information missing – ABO or Rh, product type, expiration date, unit number, volume, weight, platelet count (for platelet products)
- Label indicates testing performed, but the unit was not tested
- Unit tested but labeled incorrectly
- Unit labeled with an extended expiration date, even if it was transfused within the correct dating period
- Autologous labeling missing or shows incorrect information, such as the patient's name, social security number, or date of birth
- Unit labeled as crossmatch compatible when the unit was either not crossmatched or found incompatible
- Unit or crossmatch documents labeled with the incorrect recipient name or identification number

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- SOP's for labeling not followed or not adequate, such as:
  - Unit labeled with incorrect information indicating a special procedure was performed, such as irradiation, leukoreduction, or washing.
  - Unit not labeled with a biohazard label, when required
  - Label indicates testing performed, but the unit was not tested (e.g., unit tested anti-CMV positive, but labeled as negative)

Labeling

**DO NOT REPORT:**

- Unit labeled with a shortened expiration date
- Directed unit, suitable for allogeneic use, labeled with incorrect or missing donor information, such as name, social security number, or date of birth, if the unit is otherwise properly labeled.
- Any of the following information missing from or incorrectly stated on the label (provided the unit is otherwise acceptable): collection date, or facility identification
- Unlicensed unit labeled with a license number

**F. QUALITY CONTROL AND DISTRIBUTION**

A deviation in quality control and distribution includes deviations or unexpected events in which:

- Quality control or quality assurance procedures were not followed or not performed.
- Product was inappropriately distributed.

A biological product deviation report is required when any of the following events occur and products are distributed:

- A unit distributed that was designated to be quarantined due to
  - Unsuitable medical history
  - Incorrect or incomplete testing
  - Positive testing
  - Testing not performed or not documented
- An unsuitable unit distributed, such as:
  - Outdated product
  - Overweight or underweight unit/component
  - Clotted unit or a unit with clotted segments attached
  - Hemolyzed unit or a unit with hemolyzed segments attached
  - Unit shipped or stored at incorrect temperature
- Autologous unit was inaccurately labeled as meeting all allogeneic requirements but unit did not meet all such requirements
- Product did not meet all specifications for release, but was distributed

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- SOP's for quality control or distribution not followed or not adequate, such as:
  - Product quality control or product specifications unacceptable or not documented
  - Product distributed prior to resolution of any discrepancy in manufacturing, such as testing, labeling or donor suitability

For *transfusion services*, this also includes the distribution of products not in accordance with SOP's which may affect the safety, purity, or potency of a product, such as:

- The transfusion service receives an order for a unit requiring special processing or testing, such as irradiation, leukoreduction, CMV negative, and fails to perform that processing and distributes the unit
- Wrong unit issued for a specific patient
- The transfusion service received an order for a specific type of product, but distributes an incorrect product, such as an order for platelets is filled with Fresh Frozen Plasma
- Improper ABO or Rh type selected for patient
- Issuing the wrong filter for use in transfusion

Quality Control and Distribution

**DO NOT REPORT:**

- Unit shipped to the incorrect facility
- Discrepancy between the shipping document and the shipment as long as units are properly labeled.
- Blood establishment received an order from another facility for a specific type of product and did not fulfill the specific request, provided the unit was labeled appropriately, such as an irradiated unit or one with special antigen testing
- Donor provides information regarding post donation cold or flu symptoms and products are not quarantined
- Otherwise unsuitable product, such as an expired HLA matched platelet, released through emergency release procedures and documented appropriately
- Frozen product (e.g., Fresh Frozen Plasma) breaks during thawing and the product is discarded
- Product breaks or is damaged during shipment and the product is discarded\*
- Distribution of an unlicensed unit labeled with license number

\*Although the safety, purity, or potency of broken or damaged units may be affected, these events are rarely identified as system problems in manufacturing and are generally tied to an unusual event in shipment. FDA also notes that there is minimal risk of these units being used for transfusion or further manufacture provided the unit is discarded when the event is discovered.

*Transfusion services*

**DO NOT REPORT**

- Inappropriate administration practices by the hospital staff in transfusing the patient,
  - transfusing the wrong patient
  - transfusing a patient with the wrong unit
- Distribution of an allogeneic unit when an autologous unit was available
- Release of unit using emergency protocol, provided it was labeled appropriately

**V. REFERENCES**

1. Biological Products; Reporting of Errors and Accidents in Manufacturing Proposed Rule (62 FR 49642, September 23, 1997).
2. Biological Products: Reporting of Biological Product Deviations in Manufacturing Final Rule (65 FR 66621, November 7, 2000).
3. Memorandum to All Registered Blood Establishments: "Responsibilities of Blood Establishments Related to Errors and Accidents in the Manufacture of Blood & Blood Components," March 20, 1991.
4. Memorandum to All Registered Blood and Plasma Establishments: "Guidance Regarding Post Donation Information Reports," December 10, 1993.
5. Guideline for Quality Assurance in Blood Establishments, July 11, 1995.
6. Draft Guidance for Industry: Biological Product Deviation Reporting for Licensed Manufacturers of Biological Products Other than Blood and Blood Components.