Biological Product Deviation Reporting for Blood and Plasma Establishments

---

Guidance for Industry

This guidance is for immediate implementation.

FDA is issuing this guidance for immediate implementation in accordance with 21 CFR 10.115(g)(2) without initially seeking prior comment because the agency has determined that prior public participation is not feasible or appropriate.

FDA invites comments on this guidance. Submit one set of either electronic or written comments on this guidance at any time. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*. FDA will review any comments we receive and revise the guidance when appropriate.

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD), 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002, or by calling 1-800-835-4709 or 240-402-8010, or email ocod@fda.hhs.gov, or from the Internet at https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances.

For questions on the content of this guidance, contact OCOD at the phone numbers or email address listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
March 2020

Table of Contents

Contains Nonbinding Recommendations

Guidance for Industry

Biological Product Deviation Reporting for Blood and Plasma Establishments

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

We, FDA, are providing you, a blood or plasma establishment, with revised recommendations related to biological product deviation (BPD) reporting. This guidance document is intended to assist blood and plasma establishments in determining when a report is required, who submits the report, what information to submit in the report, the timeframe for reporting, and how to submit the report. The revised guidance explains that we do not consider post donation information (PDI) events to require BPD reports. PDI includes information that a donor, or other reliable source, provides to a blood establishment after a donation (e.g., at a subsequent donation) that would have resulted in deferral of the donor had you known the information at the time of donation.[1] The revised guidance also contains other technical updates and editorial revisions to improve clarity and provide a more streamlined document. FDA is also announcing the withdrawal of two obsolete memoranda to blood establishments entitled, "Responsibilities of Blood Establishments Related to Errors & Accidents in the Manufacture of Blood & Blood Components," issued March 20, 1991, and "Guidance Regarding Post Donation Information Reports," issued December 10, 1993.

For the purposes of this document, "blood and plasma establishment" includes licensed manufacturers of blood and blood components, including Source Plasma, unlicensed registered blood establishments, and transfusion services. This guidance document supersedes the guidance entitled "Guidance for Industry: Biological Product Deviation Reporting for Blood and Plasma Establishments," dated October 2006.

[1] Although FDA does not consider PDI events to require BPD reports under 21 CFR 606.171, FDA is aware that PDI events will continue to occur. Blood establishments are required to comply with applicable regulations regarding, among other things, establishing, maintaining, and following standard operating procedures (see 21 CFR 606.100(b)) and maintaining records (see 21 CFR 606.160). FDA will continue to assess procedures and records associated with PDI events during routine inspections of blood establishments.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Under 21 CFR 606.171,[2, 3] you are required to report certain events associated with the manufacturing, to include testing, processing, packing, labeling, or storage, or with the holding or distribution, of blood or a blood component, which may affect the safety, purity, or potency of a distributed product. Safety, purity, and potency are defined in 21 CFR 600.3(p), (r), and (s), respectively.

Under 21 CFR 606.171(c), you should submit reports as soon as possible, but you must submit reports at a date not to exceed 45 calendar days from the date of acquiring information reasonably suggesting a reportable event has occurred. To facilitate reporting, we have developed a standardized reporting format that you may submit electronically or in paper form, by mail.

You are required to evaluate and investigate, as appropriate, unexplained discrepancies and failures to meet specifications, and to maintain complaint records, including records of investigations and follow-up (21 CFR 606.100, 211.192 and 211.198). Procedures for the investigation of any unexplained discrepancy or the failure of a lot or unit to meet any of its specifications should include provisions for:

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

[2] See Ref. 1.

[3] Manufacturers of licensed biological products other than blood and blood components, including vaccines, allergenic products, therapeutics, plasma derivatives, and in vitro diagnostics (IVDs), are required to submit product deviation reports in accordance with 21 CFR 600.14, which contains requirements similar to those in 21 CFR 606.171. We have issued a separate guidance for reporting of product deviations by licensed manufacturers of biological products other than blood and blood components (Guidance for Industry: Biological Product Deviation Reporting for Licensed Manufacturers of Biological Products Other than Blood and Blood Components, October 2006) (Ref. 2).

III. REGULATORY REQUIREMENTS AND RECOMMENDATIONS

A. Who Must Report? (21 CFR 606.171(a))

Under 21 CFR 606.171, the manufacturer that had **control** over the product when the reportable event occurred must submit a report. This reporting requirement applies to:

- licensed manufacturers of blood and blood components, including Source Plasma;
- unlicensed registered blood establishments; and
- transfusion services.

We define "control" in 21 CFR 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 for compliance with current good manufacturing practices."

If you are a plasma fractionator or in vitro diagnostic (IVD) manufacturer that manufactures Source Plasma or other blood components for further manufacture into another licensed biological product (e.g., Immune Globulin Intravenous (Human), Reagent Red Blood Cells), you are subject to reporting as specified in 21 CFR 600.14(a)(2)(iii).

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., relevant transfusion-transmitted infection[4] (RTTI) or compatibility)), irradiation, blood collection, storage and distribution. If you contract out any manufacturing step, for the purposes of 21 CFR 606.171(a), that step is performed under your control. Under 21 CFR 606.171(a), you must establish, maintain, and follow a procedure for receiving information from that person (e.g., a contract manufacturer) on all deviations, complaints, and adverse events concerning the affected product.

For the purposes of 21 CFR 606.171(a), we do not consider contract manufacturing to include the supply of blood products to a transfusion service from a blood establishment or the supply of plasma to a fractionator from a blood establishment.

For the purposes of 21 CFR 606.171(a), a blood establishment that performs compatibility testing for a transfusion service and makes the final determination regarding the suitability of a product for a specific patient and distributes the product to the transfusion service is not considered a contract manufacturer. The blood establishment maintains the patient transfusion record and blood unit disposition history for the transfusion service. In this case, the blood establishment would be responsible for

[4] See 21 CFR 630.3(h).

submitting reports related to the manufacturing steps it performs. The transfusion service would be responsible for reporting events related to the manufacturing steps it performs, such as storage and distribution.

If you are a *contract manufacturer* (i.e., under contract, you perform manufacturing for another establishment), you must conduct such manufacturing in accordance with current good manufacturing practice (CGMP) (21 U.S.C. 351(a)(2)(B)), but you are not required to report BPDs to us.

Examples of who must report:

1. EVENT
   You are a blood establishment that contracts with a test laboratory to have the laboratory perform RTTI testing, including nucleic acid testing (NAT). The test laboratory did not perform the testing in accordance with the test kit manufacturer's instructions or its own procedures. The test laboratory used the incorrect incubation time. Failure to follow the test kit instructions or validated procedures may affect the safety, purity, or potency of the product.

   REPORTING
   Under 21 CFR 606.100(c), 211.192, and 211.198, the test laboratory must perform an investigation. The test laboratory is NOT required to report to us. The test laboratory would provide the blood establishment with details of the deviation in RTTI testing.

   Under 21 CFR 606.171(a), you must establish, maintain, and follow a procedure for receiving information from the test laboratory about deviations concerning the RTTI testing. Under 21 CFR 606.171(b), you must submit a report to us if you distributed the improperly tested product. We recommend that you assure that the test laboratory performed an adequate investigation.

2. EVENT
   You are a blood establishment that contracts with another blood establishment (referred to as an irradiator) to perform irradiation of blood products. You sent a product to the irradiator. After irradiation, the product was returned to you. The irradiator notified you that the incorrect dosage was used which may affect the safety, purity, or potency of the product.

   REPORTING
   Under 21 CFR 606.100(c), 211.192, and 211.198, the irradiator must perform an investigation. The irradiator is NOT required to report to us.

The irradiator would provide you with details of the deviation in the irradiation process.

Under 21 CFR 606.171(a), you must establish, maintain, and follow a procedure for receiving information from the irradiator about deviations concerning the irradiation process. Under 21 CFR 606.171(b), you must submit a report to us if you distributed the improperly irradiated product. We recommend that you assure that the irradiator performed an appropriate investigation.

3. EVENT
You are a blood establishment that distributed a blood product to another blood establishment (referred to as an irradiator), which subsequently irradiated it. The irradiator used the incorrect dosage during irradiation which may affect the safety, purity, or potency of the product.

REPORTING
Under 21 CFR 606.100(c), 211.192, and 211.198, the irradiator must perform an investigation. Under 606.171(b), the irradiator must submit a report to us if it distributed the improperly irradiated product. You are NOT required to report to us or perform an investigation because the product was not in your control at the time the event occurred, i.e., it was not irradiated under a contract manufacturing agreement.

4. EVENT
You are a transfusion service that received a unit of Platelets from a blood establishment. When you received the product, you discovered that the product was labeled with an improperly extended expiration date, which may affect the safety, purity, or potency of the product. You notified the blood establishment.

REPORTING
Under 21 CFR 606.100(c), 211.192, and 211.198, the blood establishment must perform an investigation of the labeling deviation. Under 21 CFR 606.171(b), the blood establishment must submit a report to us.

You are NOT required to report to us unless you distributed the unit without correcting the label.

5. EVENT
You are a transfusion service that received 10 units of Platelets and subsequently pooled them to create Pooled Platelets. You improperly labeled the Pooled Platelets 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, you must perform an investigation of the deviation in labeling. Under 21 CFR 606.171(b), you must submit a report to us if you distributed (i.e., issued for transfusion) the mislabeled product.

6. EVENT
You are a transfusion service that received a unit of Red Blood Cells from a blood establishment. The unit was labeled with an improperly extended expiration date (for example, 54 days instead of 42 days) but you did not recognize this before crossmatching and distributing the unit to the surgical floor. The surgical floor questioned the expiration date of the unit and returned the unit to the blood bank, at which time the improperly extended expiration date was discovered. This may affect the safety, purity, or potency of the product.

REPORTING
Under 21 CFR 606.100(c), 211.192, and 211.198, you must perform an investigation of the inappropriate release of a product with an improperly extended expiration date. Under 21 CFR 606.171(b), you must submit a report to us because the product was in your control at the time of such inappropriate release. We recommend that you notify the blood establishment of the incorrect labeling.

Under 21 CFR 606.100(c), 211.192, and 211.198, the blood establishment must perform an investigation of the deviation in labeling. Under 21 CFR 606.171(b), the blood establishment must also submit a report to us, since the product was in the blood establishment's control at the time of the labeling deviation

7. EVENT
You are a Source Plasma collection establishment that tested a unit of Source Plasma and distributed it to a fractionator. You discovered that one of the RTTI tests was incorrectly performed. Repeat testing of a reserve sample was positive for the RTTI. The safety, purity, or potency of the Source Plasma may be affected.

REPORTING
Under 21 CFR 606.100(c), you must perform an investigation of the improper testing and distribution of the unit. Under 21 CFR 606.171(b), you must submit a report to us. We recommend that you evaluate the need for product retrieval or notification to the fractionator. *Note: If your contract testing laboratory performed the testing, you would be the reporting establishment.*

The fractionator would submit a report under 21 CFR 600.14, if it used the improperly tested plasma unit in the manufacture of a licensed biological product and distributed the final product. The use of the improperly tested plasma would represent an unexpected or unforeseeable event that may affect the safety, purity, or potency of the final product (see footnote 2).

B. What Do I Report? (21 CFR 606.171(b))

Under 21 CFR 606.171(b), you must report any event, and information relevant to the 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 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 with you; and

(3) involves distributed blood or blood components.

An adequate procedure for deviation reporting (21 CFR 606.100(b)) should include steps for determining whether an event is one for which a report must be submitted. The decision to report should be based on whether the event had the **potential** to affect the safety, purity, or potency of a product. The terms safety, purity, and potency are defined in 21 CFR 600.3(p), (r), and (s), respectively.

Retrieval, Consignee Notification and Lookback

You are not required to submit a BPD report simply because you failed to follow your own internal procedures for retrieval, notification or lookback (e.g., you do not have to submit a report if you did not notify consignees within the time frame prescribed in your procedures). The failure to follow retrieval, notification, or lookback procedures does not, by itself, affect the safety, purity, or potency of the product. However, you must submit a report if the underlying reason for the retrieval, notification, or lookback meets the reporting criteria in 21 CFR 606.171(b). In that case, the report must describe the event that may have affected the safety, purity, or potency of the distributed product. For example, you distributed a product inappropriately collected from a donor with a history of high-risk behavior, which may affect the safety, purity, or potency of the product. You did not notify consignees within the timeframe described in your internal

procedures. You are not required to report the failure to follow your internal consignee notification procedures; however, you are required to report the improper release of the product.

You are **not** required to submit a report:

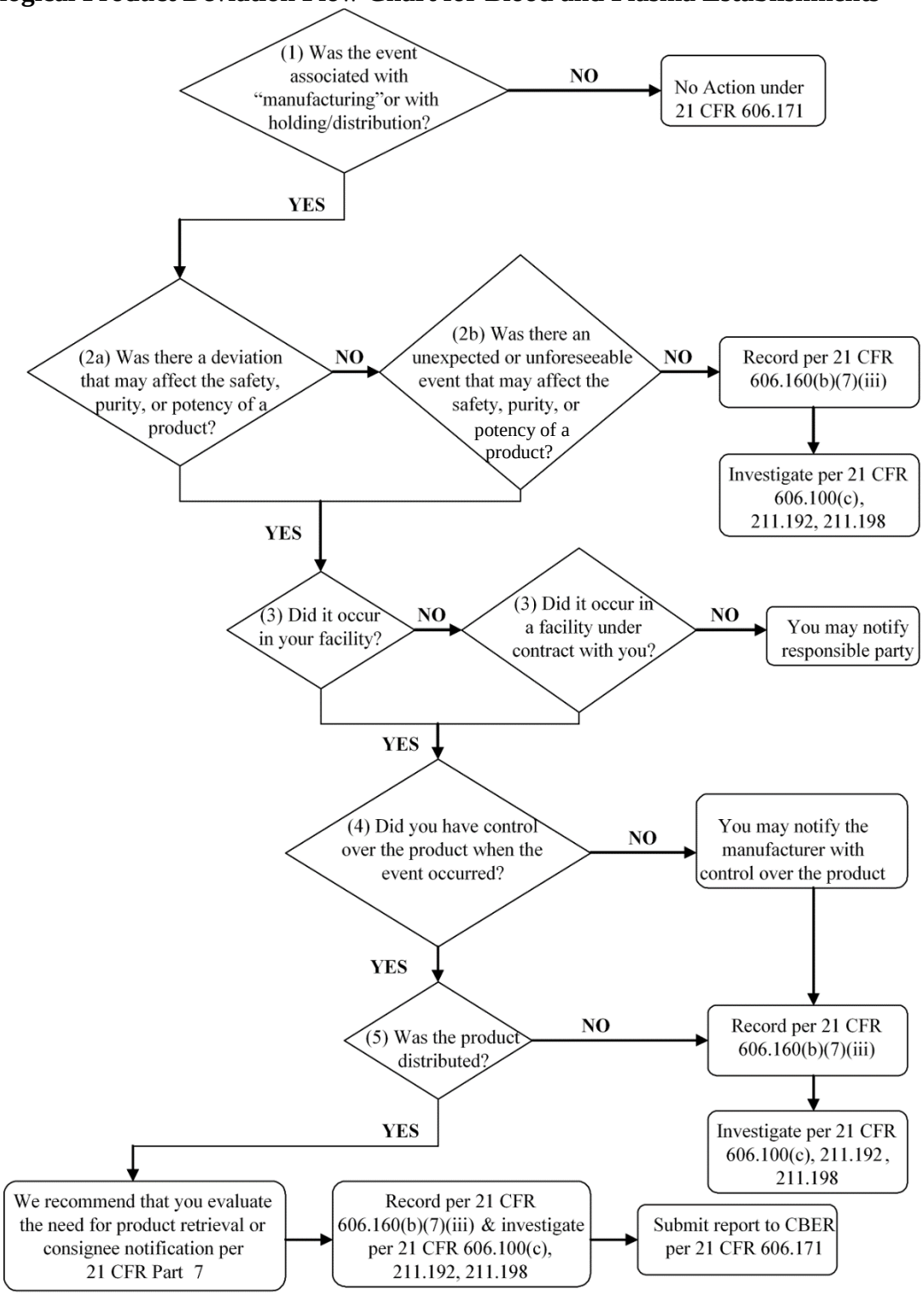
1. When you did not distribute potentially affected products, regardless of the event.
2. When you determined, prior to distributing the product, that the event did not actually affect the safety, purity, or potency of the product.
3. When you detected the event and prior to distribution, made the appropriate corrections.
4. When the event was related to donor safety only and did not have the potential to affect the safety, purity, or potency of the product.
5. If your report would simply state that you were late in reporting the event to us.
6. If you receive information, after a donation, that would have resulted in deferral of the donor had you known the information at the time of the donation (post donation information).
7. If you receive information of a post donation illness.
8. For a recordkeeping deviation that would not affect the safety, purity, or potency of the product.

While the above examples would not be reportable under 21 CFR 606.171, the events may constitute deviations from the regulations, which we would assess during inspection.

Biological Product Deviation Reporting Flow Chart for Blood and Plasma Establishments

You may use the following flow chart to help you determine if you are required to report an event to us.

Biological Product Deviation Flow Chart for Blood and Plasma Establishments[5]



[5] For purposes of this flowchart, and the corresponding discussion below regarding the questions in this flowchart, an "event" is a deviation from current good manufacturing practice, applicable regulations, applicable standards, or established specifications, or an unexpected or unforeseeable event.

The following questions correspond to the flow chart:

(1) Was the event associated with "manufacturing" or holding or distribution as they are described in the regulation?

As described in 21 CFR 606.171(b), manufacturing includes testing, processing, packing, labeling, or storage. In addition, you must report events associated with the holding or distribution of both licensed and unlicensed blood or blood components, including Source Plasma.

Under 21 CFR 606.171, you are not required to report events that occur after you distribute the product, including those related to the administration of blood or blood components.

Examples

1. A *Transfusion Service* is NOT required to report to us 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:

- If the transfusion service issued a product from the laboratory to the nursing floor, operating room or emergency room, etc., for transfusion and the product was not held at the appropriate temperature outside of the transfusion service prior to transfusion. However, the transfusion service is required to report if the product was returned and the transfusion service reissued the product despite determining it to be unsuitable.

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

- If the transfusion service issued a filter with the product and the hospital staff did not use the filter at the bedside.

- If the patient has a transfusion reaction that is not related to an event in manufacturing. Fatalities due to Transfusion Related Acute Lung Injury (TRALI) or other transfusion complications must be reported to CBER in accordance with 21 CFR

606.170(b). We also accept voluntary reports of non-fatal TRALI as a serious adverse reaction to transfusions. Such voluntary reports can be submitted via MedWatch (see FDA's website at https://www.accessdata.fda.gov/scripts/medwatch/index.cfm?action=reporting.home.
For additional information related to TRALI, see the "Dear Colleague" letter published October 19, 2001 at https://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/BloodSafety/ucm095556.htm.

2. A *Blood Establishment* is NOT required to report if the event is not associated with its manufacturing process and did not occur while the product was under the control of the blood establishment. For example, a report is not required:

- If the blood establishment distributed a product to a transfusion service and the transfusion service stored the product at the incorrect temperature. However, under 21 CFR 606.171(b), if the transfusion service distributed the product, the transfusion service must report to us.

- If the blood establishment received an unacceptable product (for example, a hemolyzed unit) from another blood establishment, identified the discrepancy and returned or discarded the product. Under 21 CFR 606.171(b), the blood establishment that distributed the unacceptable product, but not the establishment that received and returned or discarded it, must report to us.

(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 could prevent a product from meeting all CGMP requirements, applicable standards, and established specifications. The CGMP requirements and applicable standards for blood and blood components are currently found in 21 CFR Parts 210, 211, 600, 606, 610, 630, and 640.

(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 you followed all required procedures, something unanticipated occurred that may affect the safety, purity, or potency of a product. This may be due to information

that you did not have at the time of manufacturing. The following is an example of an unexpected or unforeseeable event in which the safety, purity, or potency may be affected:

- After you distributed a product, your materials vendor informed you that materials used in the collection or processing of blood and blood components, such as reagents, soft goods, software, or the collection device, did not meet all requirements or specifications, and you could not have detected the problem during your routine incoming material qualification procedures.

If an event occurred, but could not have affected the safety, purity or potency of a product, you must record and investigate the event in accordance with 21 CFR 606.160(b)(7)(iii), 606.100(c), 211.192 and 211.198, but you do not need to report to us.

*Under 21 CFR 606.171(b), if you discover an event that may affect safety, purity, or potency of the product **after** you have distributed a product, you must report the event, regardless of whether consignee notification or product retrieval is necessary. You must report the event even if you ultimately determine, through investigation after distribution, that the safety, purity or potency of the product was not affected.*

For example, if you distributed a product that was not tested for RTTI, you must submit a report to us under 21 CFR 606.171(b), even if you subsequently tested the product and found it to be negative

*If you discover an event **prior** to distribution of a product and determined that the event did not affect the safety, purity, or potency of the products, you are not required to report under 21 CFR 606.171.*

For example, if you discovered a deviation in testing prior to the distribution of a product and you appropriately retested a donor blood sample collected at the same time as the product and found it to be negative, you are not required to report to us under 21 CFR 606.171.

(3) Did the event occur in your facility or in a facility under contract with you?

You are required to submit a report if the event occurred within your facility or a facility under contract to perform a manufacturing, holding, or distribution step, such as a testing laboratory. Under 21 CFR 606.171(a) and (b), you must report events that occur at the contract facility and 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 would notify the manufacturer(s) with control over the product, if its products may be affected. You are not responsible for reporting the event to us.

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

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

You have "control," as defined in 21 CFR 606.3(l), 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 CGMP.

You are responsible for reporting if you had control over the product when the event occurred, and you 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, maintain, and follow a procedure for receiving information from the contract manufacturer 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 us under 21 CFR 606.171.

(5) Was the product distributed?

We define "distributed" in 21 CFR 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.

If you are a licensed blood establishment, a product is considered distributed when you ship the product to another facility or broker that is not part of your license or issue the product to staff outside the blood establishment for transfusion. A product is **not** considered distributed if it was shipped from one location to another and both locations are under the same license.

If you are an unlicensed blood establishment, including a transfusion service, a product is considered distributed when you issue the product to staff outside of the blood establishment for transfusion or you ship it to another facility or broker.

If you collect Source Plasma or other products for further manufacture, the product is considered distributed when you release or ship the product for further processing. Distribution includes shipment to a plasma broker. Distribution does not include shipment to an off-site storage facility if the product is still under your control.

Examples:

- If a blood establishment labeled a product with an improperly extended expiration date and distributed it to a transfusion service, under 21 CFR 606.171(b) the blood establishment must report to us.

- If a transfusion service received 10 units of platelets from a blood establishment, pooled the platelets, mislabeled the final Pooled Platelet container with an improperly extended expiration date, and issued the product to the nursing staff for transfusion, under 21 CFR 606.171(b) the transfusion service must report to us. However, if the transfusion service detected and corrected the expiration date before distributing the product, under 21 CFR 606.160(b)(7)(iii), 606.100(c), 211.192, and 211.198, the transfusion service must document and investigate the deviation but is not required to report to us.

If you distributed the product, we recommend that you also assess the need for product retrieval or consignee notification in accordance with 21 CFR Part 7. You must document the event in accordance with 21 CFR 606.160(b)(7)(iii) and investigate in accordance with 21 CFR 606.100(c), 211.192 and 211.198, regardless of whether you distributed the product.

C. When Do I Report? (21 CFR 606.171(c))

Under 21 CFR 606.171(c), you should report a BPD as soon as possible, but you must report at a date not to exceed 45 calendar days from the date that you, your agent, or another person who performs a manufacturing, holding, or distribution step under your control, 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 assess whether the event had the potential to affect the safety, purity, and potency of products and determine the status of the products (i.e., whether they have been distributed or need to be quarantined).

If you contract with a facility to perform a manufacturing, holding, or distribution step and an event occurs at the contractor, the time period for reporting starts when your contractor learns about the event.

D. How and Where Do I Report? (21 CFR 606.171(d) and (e))

Under 21 CFR 606.171(d), you must use Form FDA-3486 to report BPDs. You must submit the completed report either electronically through CBER's web site at https://www.fda.gov/vaccines-blood-biologics/report-problem-center-biologics-evaluation-research/biological-product-deviations or by mail to:

Food and Drug Administration
Center for Biologics Evaluation and Research
Document Control Center
10903 New Hampshire Avenue
Silver Spring, Maryland 20993-0002

If the event occurred at your contract manufacturer, we recommend that you include in the report the details reported to you by the contract manufacturer regarding the event.

Complete a separate report for each event. If an event involves more than one product, you only need to complete one report listing all distributed products affected.

The Form FDA-3486 and instructions for completing both formats are located at https://www.fda.gov/vaccines-blood-biologics/report-problem-center-biologics-evaluation-research/biological-product-deviations.

IV. EXAMPLES OF REPORTABLE AND NON-REPORTABLE EVENTS BY MANUFACTURING SYSTEM

We categorize BPD reports according to where in the manufacturing system the event occurred. Following the bulleted list below, each system is explained further, and we provide examples of both reportable and non-reportable events. An event may be the result of a failure within a variety of systems. It is important for you to know both where the event occurred and why your product was allowed to continue through the manufacturing process and be distributed, so that you can implement the appropriate corrective action to prevent recurrence.

- A *donor eligibility event* occurs in the donor eligibility process (for example, donor screening, and donor deferral procedures) (see section IV.A of this guidance).

- A *collection event* occurs during the collection process (see section IV.B of this guidance).

- A *component preparation event* occurs during the component preparation process (see section IV.C of this guidance).

- A *testing event* occurs during the testing process and includes sample deviations and unexpected events (see section IV.D of this guidance).

- A *labeling 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 of this guidance).

- A *quality control and distribution event* involves a failure in either the quality control (QC) or distribution systems. This category includes the distribution of a product that did not meet specifications (see section IV.F of this guidance).

The following examples of events are not all-inclusive and do not represent all variations that may occur. The examples include deviations from CGMP, applicable regulations, applicable standards, and established specifications, in addition to unexpected or unforeseeable events. Not all of these examples will necessarily apply to you or to all products you manufacture.

A. Donor Eligibility

Donor eligibility events are those that occur during donor screening or donor deferral which you did not discover until after you distributed the product.

This category includes events concerning the medical history interview or physical assessment, blood donor record documentation, and deferral process.

1. Medical history interview process

   Under 21 CFR 606.171(b), you must submit a report when there is an event (a deviation or unexpected or unforeseeable event) that occurs during the medical history interview process that may affect the safety, purity, or potency of a product you **distributed.** Examples of reportable events associated with the interview process may include:

   - Donor provided information that warranted deferral, but the donor was inappropriately determined eligible.

- Donor provided incomplete information that was not resolved by follow-up questioning, and the donor was inappropriately determined eligible.

2. Physical assessment

Under 21 CFR 606.171(b), you must submit a report when there is an event (a deviation or unexpected or unforeseeable event) that occurs during the physical assessment that may affect the safety, purity, or potency of a product you **distributed.** Examples of reportable events associated with the physical assessment may include:

- Donor's hemoglobin or hematocrit was unacceptable.
- Donor's temperature was unacceptable.
- Plateletpheresis donor had an unacceptable platelet count and there was no documented platelet count for the product.
- Physical assessment was not performed or was inadequate.

3. Donor record documentation

Under 21 CFR 606.171(b), you must submit a report when there is an event (a deviation or unexpected or unforeseeable event) in donor record documentation that may affect the safety, purity, or potency of a product you **distributed.** Examples of reportable events associated with donor record documentation may include:

- No documentation of donor's hemoglobin, hematocrit, temperature, arm inspection.
- Answers to the donor history questions, including high risk questions, were missing or incomplete, except those only affecting donor safety (e.g., history of pregnancy or heart disease).
- Donor record was incomplete or incorrect

4. Deferral process

Under 21 CFR 606.171(b), you must submit a report when there is an event (a deviation or unexpected or unforeseeable event) during the deferral process that may affect the safety, purity, or potency of a product you **distributed.** Examples of reportable events associated with the deferral process, where the donor subsequently donated, may include:

- Donor was incorrectly omitted from the deferral list.
- Deferral list contained inaccurate information, such as temporary deferral instead of permanent deferral.
- The donor tested positive for an RTTI, and an appropriate reentry algorithm was not followed.

- Incorrect donor identification information was used to check the deferral list (regardless of whether the donor was previously deferred). You would report even if the donor provided discrepant identification information, such as different names on two donations –for example, J. Michael Smith and James M. Smith.
- The deferral list was not checked (regardless of whether the donor was previously deferred).

DO NOT REPORT:

- Autologous donor did not meet the eligibility criteria and the medical director authorized acceptance of the donor in accordance with 21 CFR 630.20(a), provided the product was labeled appropriately and not crossed over for allogeneic use.
- Donor did not meet eligibility criteria related to donor safety only, such as donor's weight, age, or donation frequency. These criteria do not affect product quality.
- Plateletpheresis donor had an unacceptable platelet count, but the platelet count performed on the product was acceptable.
- The record of deferred donors was not checked, or incorrect information was used to check record of deferred donors and you determined **prior to distribution** of products from that donation that the donor was not previously deferred.
- Donor was accepted on the basis of incomplete information and you obtained additional information from the donor, **prior to distribution** of any products, demonstrating that the donor was acceptable.
- Donor was deferred, and no products were collected. Donor was not placed on the deferral list, but the donor did not have subsequent donations, therefore there were no products affected.
- Reports of PDI.

B. Collection

Collection events include those that occur during the collection process, which you did not discover until after you distributed the product

Under 21 CFR 606.171(b), you must submit a report when there is an event (a deviation or unexpected or unforeseeable event) during the collection process that may affect the safety, purity, or potency of a product you **distributed.** Examples of reportable events associated with the collection process may include:

- Product was contaminated or potentially contaminated with bacteria or air. (The manufacturer that had control of the product during collection would be responsible for reporting this.)

- 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.
- Donor was over bled, and the product was distributed as Whole Blood. (Product may be affected if there was an inadequate volume of anticoagulant in the collection bag.)
- *Product was discovered to be clotted.
- **Product was discovered to be hemolyzed.

** The manufacturer who had control of the product during collection would be responsible for reporting clotted products that were distributed.*
***The manufacturer who had control of the product during collection, component preparation and storage would be responsible for reporting hemolyzed products that were distributed and were not accepted into the consignee's inventory. A transfusion service would be responsible for reporting hemolyzed products if the product was inspected upon receipt from the collection facility and found acceptable (no hemolysis) and then later found to be hemolyzed while in the control of the transfusion service and subsequently distributed (reported under QC & Distribution system).*

DO NOT REPORT:

- A recordkeeping deviation that would not affect the safety, purity, or potency of the product, such as the identification of the phlebotomist was missing from the donor record.
- Donor has a reaction during the collection procedure. If the donor has a fatal reaction as a result of a complication of blood collection, a BPD report is not required, 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 events include those that occur during the preparation or processing of a product, which you did not discover until after you have distributed the product.

Under 21 CFR 606.171(b), you must submit a report when there is an event (a deviation or an unexpected or unforeseeable event) during the component preparation process that may affect the safety, purity, or potency of a product you **distributed.** Examples of reportable events associated with the component preparation process may include:

- 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. (The manufacturer that had control of the product during the component preparation process would be responsible for reporting this.)
- Component was not manufactured according to established procedures such as:
  - Platelets were prepared from a Whole Blood product collected from a donor who took aspirin or other drugs that affect platelet function and the unit was not labeled to identify the ingested drug that adversely affects platelet function;
  - Fresh Frozen Plasma or Cryoprecipitated AHF did not meet freezing time requirements;
  - Component manufactured from a Whole Blood unit that did not meet specifications, such as;
    - Overweight or underweight Whole Blood unit,
    - Whole Blood unit was stored at unacceptable temperature,
  - Incorrect filter was used for leukoreduction;
  - Product was not leukoreduced within the appropriate time frame;
  - Incorrect dosage was used for irradiation;
  - Product was not washed/deglycerolized properly.

DO NOT REPORT:

- The signature of the person preparing the product was missing.

D. Testing

Testing events include those that occur during the testing process which you did not discover until after you distributed the product. Testing includes all tests used to assure the safety, purity, and potency of a product (e.g., testing requirements in 21 CFR 610.40, 640.5, and 606.151). Use of unsuitable or inappropriate samples may be testing deviations or unexpected events.

Under 21 CFR 606.171(b), you must submit a report when there is an event (a deviation or unexpected or unforeseeable event) during testing that may affect the safety, purity, or potency of a product you **distributed.** Examples of reportable events associated with testing may include:

- Testing was not performed in accordance with test manufacturer's instructions, such as
  - Incorrect incubation time or temperature was used;
  - Incorrect reagent was used/licensable components from two different test kit lots were used;

  - Incorrect addition of reagents (incorrect sequence, volume or concentration).
  - Initial reactive was not repeated in duplicate (RTTI testing), when required by test manufacturer's instructions.
- Testing was incomplete, not performed, or not documented.
- Sample was tested not in accordance with the manufacturer's package insert (e.g., repeated testing until you obtained negative result).
- Test results were inappropriately invalidated.
- Sample that did not meet specifications for testing was used, such as
  - Sample was improperly stored;
  - Sample was diluted (for example, diluted with saline after an apheresis procedure);
  - Sample was labeled with the wrong donor or patient identifier.
- Testing was performed using a reagent or test kit in which QC was unacceptable or not documented. This may include situations in which QC testing was not performed or was not documented on one day, even if the QC testing the day before and the day after was acceptable.
- Testing was performed using expired reagents.

For *transfusion services*, reportable events may include:

- Patient samples were mislabeled or collected from the wrong patient and were used to perform pretransfusion testing and a product was distributed based on that testing. This may include samples collected by transfusion service personnel and personnel outside of the blood establishment.
- Patient typing results or compatibility testing results were misinterpreted, and a product was distributed based on that testing.
- Antibody screen or identification testing on recipient, as set forth in your procedures, was not performed or was incomplete prior to distribution of product.
- Product with no historical antigen typing was not tested for an antigen which corresponds to the patient's antibody, as set forth in your procedures.
- Immediate spin crossmatch was performed when a patient's history or testing results indicated that an indirect antiglobulin test is needed.

DO NOT REPORT:

- You appropriately invalidated results of an assay and you retested samples and they tested negative before the product was distributed.

E. Labeling

Labeling events include those that occur during the labeling process, which you did not discover until after you distributed the product. Labeling events include incorrect, missing or misleading information on any product labeling, including:

- the container label;
- tie tags
- the circular of information;
- the labeling accompanying the product that identifies the patient for whom it has been crossmatched (transfusion record).

Under 21 CFR 606.171(b), you must submit a report when there is an event (a deviation or unexpected or unforeseeable event) during labeling that may affect the safety, purity, or potency of a product you **distributed.** Examples of reportable events associated with labeling may include:

- Labeling contains an incorrect ABO group or Rh type, antigen type, antibody, anticoagulant, volume or expiration date.
- Information is missing from the labeling–such as ABO group or Rh type, expiration date, or volume.
- Labeling indicates additional testing was performed, but the product was not tested as described in the labeling (for example, for CMV).
- Product was tested but labeling showed testing information that is not consistent with the test results.
- Labeling indicates an incorrectly extended expiration date, even if the product was transfused within the correct dating period.
- Labeling indicates the product is crossmatch compatible when the product was either not crossmatched or was found to be incompatible.
- Labeling indicates incorrect recipient name or identification number.
- Labeling indicates an incorrect or missing donor/unit number.
- Labeling indicates an incorrect product name or product name is missing, for example:
  - Apheresis Platelets labeled as Plasma;
  - Red Blood Cells labeled as Irradiated Red Blood Cells;
  - Red Blood Cells labeled as Red Blood Cells Leukocytes Reduced, but product was not leukoreduced.

DO NOT REPORT:

- Labeling indicated a shortened expiration date
- Provided the product is otherwise acceptable and the expiration date is correct, do not report missing or incorrect collection date or facility identification.
- Unlicensed product incorrectly labeled with a US license number.

F. Quality Control (QC) and Distribution

Under 21 CFR 606.171(b), you must submit a report when there is an event (a deviation or unexpected or unforeseeable event) during or related to QC procedures or in the quarantine and distribution process that may affect the safety, purity, or potency of a product you **distributed.** Examples of reportable events associated with QC or distribution process may include:

- The distribution of a product that was processed using an instrument or reagent for which QC was unacceptable, not documented or not performed. For example:
  - No documentation that weekly QC was performed, even if daily QC tasks were performed and documented;
  - No documentation of daily QC of trip scales used to weigh whole blood collections, unless the product was weighed prior to distribution and found acceptable.
- The distribution of a product in which QC testing was unacceptable, not performed, not documented, or incomplete. For example:
  - pH (monthly QC of platelets);
  - Platelet count.
- Inappropriate release from quarantine, and distribution of, a product which was identified as not meeting specifications due to a deviation or unexpected event in donor eligibility, collection, component preparation, testing, or labeling. For example:
  - Failure to quarantine and distribution of a unit collected from a donor that was determined to be ineligible due to unacceptable donor medical history;
  - Failure to quarantine and distribution of a unit/component that was overweight or underweight;
  - Failure to quarantine and distribution of a component prepared from a Whole Blood unit in which one of the components was determined to be clotted or hemolyzed;
  - Product was released from electronic or physical quarantine and distributed prior to determining whether the product was suitable for distribution;
  - The distribution of a product prior to resolution of a discrepancy in manufacturing, such as testing, labeling or donor eligibility;
  - The inappropriate distribution of unit with a positive test result.
- The distribution of an outdated product;
- Events associated with the storage or shipment of the product, for example:
  - The product was not shipped at the appropriate temperature (e.g., the product was packed without ice for shipment);
  - The product was not stored at the appropriate temperature prior to distribution;

  - No documentation that the product was stored at the appropriate temperature, including reissuance of the product without a record of proper temperature maintenance;
  - Visual inspection was not performed or documented prior to distribution.
- Licensed establishments: You made a change from what is in your approved biologics license application (BLA) and you did not comply with the requirements of 21 CFR 601.12 (e.g., distributed products prior to approval of a supplement), if the change may affect the safety, purity or potency of the product. (see, "Guidance for Industry: Changes to an Approved Application: Biological Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture," December 2014 (Ref. 3)).
- Donor was identified as a source of transfusion-transmitted infection such as, hepatitis B or C, HIV, malaria, babesiosis, West Nile virus.
- Donor tested negative and products were distributed. The donor returned for another donation and tested positive by testing under 21 CFR 610.40 for an RTTI described in 21 CFR 630.3(h), **and** for which lookback is conducted.[6]

For *transfusion services*, reportable events may include the following:

- Incorrect product or unit issued for a specific patient (unless the transfusion service notified the hospital staff that the product ordered was unavailable and that the transfusion service was providing a substitute):
  - Special processing or testing requested, such as leukoreduced, irradiated, cytomegalovirus (CMV) negative, but product didn't meet specification
  - Product issued that was designated for different patient
  - Incorrect product type issued, such as Platelets instead of Fresh Frozen Plasma
- Product with the improper ABO or Rh type was selected for a patient.
- Visual check of product was not performed or not documented prior to distribution.
- Product was received from a blood establishment, accepted into the transfusion service's inventory and subsequently discovered to be hemolyzed after distribution.

DO NOT REPORT:

- Product was shipped to the incorrect facility.
- Product is properly labeled but the shipping invoice differs from the actual shipment.

[6] See 21 CFR 610.46 for HIV lookback requirements and 21 CFR 610.47 for HCV lookback requirements. FDA has also issued guidance documents with recommendations relating to lookback procedures (e.g., quarantine and retrieval with subsequent consignee notification) for other RTTIs (see, e.g., Guidance for Industry, *Recommendations for Reducing the Risk of Transfusion-Transmitted Babesiosis* (May 2019)). Additional guidance documents are available at https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/blood-guidances.

- Blood establishment shipped an order to another blood establishment for a specific type of product, but did not fulfill the specific request, and the product was properly labeled **and not labeled for a specific patient**. For example, an order for Red Blood Cells Irradiated was filled with a unit of Red Blood Cells that was properly labeled as Red Blood Cells.
- Otherwise unsuitable product, such as an expired human leukocyte antigen (HLA) matched platelet, was issued through emergency release and documented appropriately (see 21 CFR 606.160(b)(3)(v)).
- Frozen product (e.g., Fresh Frozen Plasma) container broke during thawing and the product was discarded.
- Product broke or was damaged during shipment and the product was discarded.[*]
- Licensed establishments: You made a change in what was approved in your BLA to appear on your product container labels, and you did not submit the change for review in accordance with 21 CFR 601.12(f), provided the change does not affect the safety, purity or potency of the product (for example, you changed your legal name or added a "doing business as" secondary name on your labels).
- A segment was found to be clotted or hemolyzed, but the product was subsequently evaluated for clots or hemolysis and found acceptable.
- Small residual clots were found in the filter after product was completely transfused, unless you did not adequately evaluate the unit for clots prior to issuing unit for transfusion.
- No documentation of instrument or reagent QC if there was data from another source that showed the instrument or reagent was acceptable, for example:
  - No documentation of acceptable reagent storage temperature, but reagent QC was documented to be acceptable;
  - Temperature was not documented on recording chart, but manual temperature readings that were documented are acceptable.
- Recipient identified with transfusion-transmitted infection, but donor was ruled out as source of transfusion-transmitted infection and donor eligibility (e.g., screening, testing) was acceptable.

[*]*Broken or damaged products are rarely identified as system problems in manufacturing and are generally tied to an unusual event in shipment.*

For *transfusion services,* non-reportable events may include:

- Inappropriate administration practices by the hospital staff in transfusing the patient; for example:
  - Hospital staff transfused the wrong patient;
  - Hospital staff transfused the patient with the wrong product or unit;

  - Hospital staff transfused the patient without using the appropriate filter.
- Allogeneic product was distributed when an autologous product was available.
- Product was distributed using an emergency protocol, provided it was labeled appropriately.

V. REFERENCES

1. Biological Products: Reporting of Biological Product Deviations in Manufacturing; Final Rule (65 FR 66621, November 7, 2000). Available at https://www.govinfo.gov/content/pkg/FR-2000-11-07/pdf/00-28133.pdf.

2. Guidance for Industry: Biological Product Deviation Reporting for Licensed Manufacturers of Biological Products Other than Blood and Blood Components, October 2006. Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/biological-product-deviation-reporting-licensed-manufacturers-biological-products-other-blood-and.

3. Guidance for Industry: Changes to an Approved Application: Biological Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture, December 2014. Available at https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM354668.pdf.