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Secretary, DOH: Umair A. Shah, MD, MPH
Acting Health Officer: Scott Lindquist, MD
Director, PHL: Romesh Gautom, PhD
Program Manager, MTS: Jessica Holloway
Survey & Investigation Manager, MTS: Lori Eschenbacher
Editor & Circulation: Chuck Talburt

Comments, letters to the editor, information for publication, and requests for subscription can be directed to:
ELABORATIONS
1610 NE 150th St
Shoreline, WA 98155
e-mail address: chuck.talburt@doh.wa.gov
NOTE: Letters to the editor may be published unless specified otherwise by the author.

Website access:
Department of Health
Medical Test Site Program
Public Health Laboratories

Inside This Issue

FDA's Guidance: "Biological Product Deviation Reporting for Blood – Guidance for Industry" and Adverse Reactions and Transfusion-Related Fatality Reporting

The Food and Drug Administration (FDA) published guidance to help blood and plasma establishments identify and submit Blood and plasma Product Deviations (BPD). This publication guides the site in determining:

- when a report is required
- who should submit the report
- what information to submit in the report
- when to submit the report, and
- how to submit the report

This article references scenarios that may occur in a transfusion services site from the FDA's "Biological Product Deviation Reporting for Blood – Guidance for Industry" and "Adverse Reactions and Transfusion-related Fatality Reporting". [References 1,2,3,4,5]. For detailed information about transfusion services, donor collection and donor testing, please see the full guidance at https://www.fda.gov/media/70694/download

The Medical Test Site Program requires that facilities performing immunohematology testing, blood product transfusions, and/or blood product storage have a policy for blood product deviation and fatality reporting.

When is a blood product deviation report required?
Under 21 CFR 606.171 you are required to report certain events associated with the following that may affect the

safety, purity or potency of a distributed blood or blood component:

- manufacturing (including testing, processing, packing, and labeling)
- storage
- holding or distribution

Safety, purity, and potency are defined in 21 CFR 600.3(p), (r), and (s), respectively as follows:

- The word *safety* means the relative freedom from harmful effect to persons affected, directly or indirectly, by a product when prudently administered, taking into consideration the character of the product in relation to the condition of the recipient at the time.
- *Purity* means relative freedom from extraneous matter in the finished product, whether or not harmful to the recipient or deleterious to the product. *Purity* includes but is not limited to relative freedom from residual moisture or other volatile substances and pyrogenic substances.
- The word *potency* means the specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to affect a given result.

Who must report a biological product deviation (BPD)?

Individuals or establishments who have "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."

What information do I report to the FDA?

Under 21 CFR 606.171(b), you must report any event, and information about 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:

- Either:
  - Represents a deviation from CGMP, applicable regulations, applicable standards, or established specifications that may affect the **safety, purity, or potency of that product**; or
  - Represents an unexpected or unforeseeable event that may affect the **safety, purity, or potency of that product**; and
- occurs in your facility or a facility under contract with you; and
- involves distributed blood or blood components.

When do I submit a report?

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

How and where do I submit a report?

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 website 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

Instructions for completing both formats are located at https://www.fda.gov/vaccines-blood-biologics/report-problem-center-biologics-evaluation-research/biological-product-deviations.

Note: Use the FDA's list of BPD Codes to assign a specific code to a reportable event when you submit the report to the FDA. This list is found at https://www.fda.gov/media/107935/download.

The FDA has listed the following examples of reportable and non-reportable events at (please see the full guidance for additional examples and information) Guidance for Industry: Biological Product Deviation Reporting for Blood and Plasma Establishments (fda.gov):

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). The 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.**

REPORT THE FOLLOWING TESTING DEVIATIONS:

When testing was not performed in accordance with test manufacturer's instructions, such as:

- Incorrect incubation time or temperature was used.
- Incorrect reagent/licensable components from two different test kit lots were used.
- Incorrect addition of reagents (incorrect sequence, volume or concentration).
- 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 a sample that was improperly stored.
- 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.
- 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.

Quality Control (QC) and Distribution Deviations

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.

Report the following QC and distribution deviations

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 or 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.

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 a 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.
- 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.

Do not report the following distribution deviations

- 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. Note: If a complication of a transfusion was confirmed to be fatal, the facility that performed the compatibility testing must submit **a fatality report** (rather than a blood product deviation report) to FDA in accordance with 21 CFR 606.170(b). See the "Adverse Reactions and Transfusion Related Fatalities" section below.
- 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 unrelated 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. You can submit a voluntary report via MedWatch. For additional information related to TRALI and biologics safety, see the "Dear Colleague" letter published October 19, 2001.
- The product was shipped to the incorrect facility.
- The product is properly labeled but the shipping invoice differs from the actual shipment.
- The frozen product (e.g., fresh frozen plasma) container broke during thawing and the product was discarded.
- The product broke or was damaged during shipment and the product was discarded. *
- 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.

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

Adverse reactions and transfusion-related fatalities

21 C.F.R. 606.170 Adverse reaction file

(a) Records shall be maintained of any reports of complaints of adverse reactions regarding each unit of blood or blood product arising as a result of blood collection or transfusion. A thorough investigation of each reported adverse reaction shall be made. A written report of the investigation of adverse reactions, including conclusions and follow-up, shall be prepared and maintained as part of the record for that lot or unit of final product by the collecting or transfusing facility. When it is determined that the product was at fault in causing a transfusion reaction, copies of all such written reports shall be forwarded to and maintained by the manufacturer or collecting facility.

(b) When a complication of blood collection or transfusion is confirmed to be fatal, the Director, Office of Compliance and Biologics Quality, CBER, must be notified by telephone, facsimile, express mail, or electronically transmitted mail as soon as possible. A written report of the investigation must be submitted to the Director, Office of Compliance and Biologics Quality, CBER, by mail, facsimile, or electronically transmitted mail (for mailing address, see § 600.2(a) of this chapter), within 7 days after the fatality by the collecting facility in the event of a donor reaction, or by the facility that performed the compatibility tests in the event of a transfusion reaction.

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.

References

1. **Biological Product Deviation Reporting for Blood and Plasma Establishments *Guidance for Industry*** March 2020. Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/biological-product-deviation-reporting-blood-and-plasma-establishments

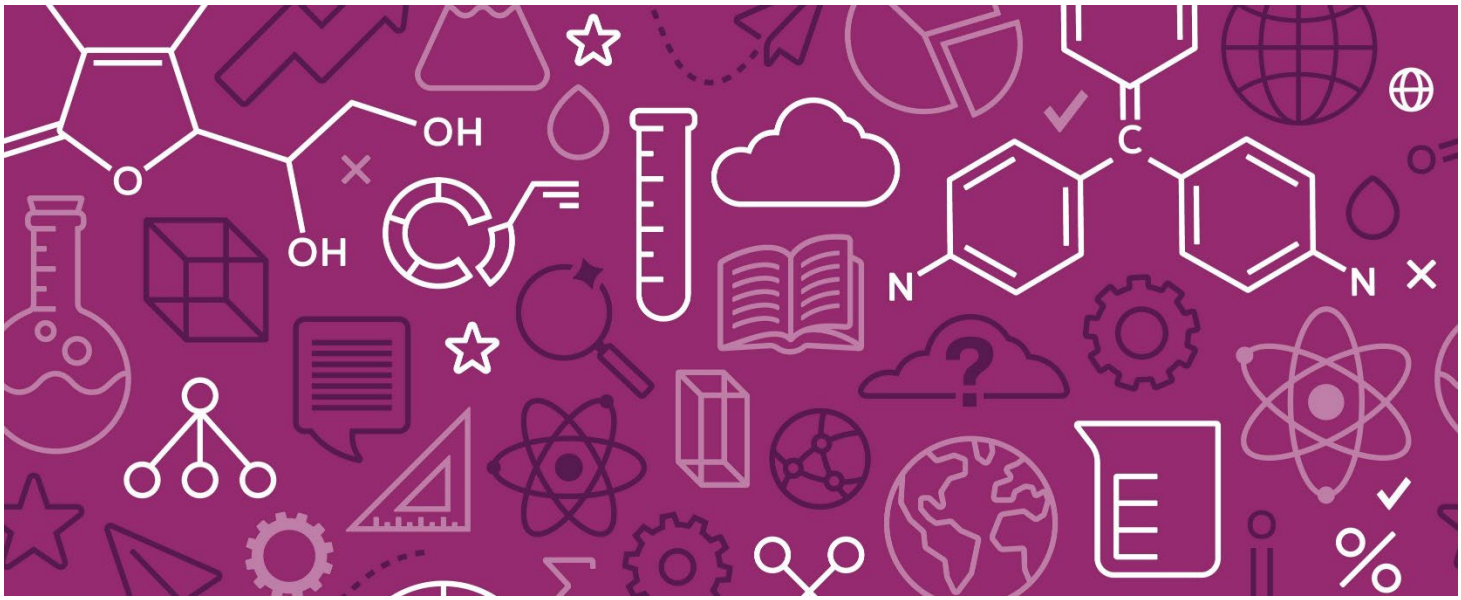
2. **Electronic Code of Federal Regulations April 22, 2020**. Available at https://www.ecfr.gov/cgi-bin/retrieveECFR?gp=1&SID=257aa01dfced31a86d37a34997c1baa2&ty=HTML&h=L&mc=true&r=PART&n=pt21.7.600#se21.7.600_13

3. **Biological Product Deviation Reporting for Blood and Plasma Establishments**

Guidance for Industry U.S. Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research, March 2020. Available at https://www.fda.gov/media/70694/download

4. **FDA: Biological Product Deviation Reporting and HCT/P Deviation Reporting** Deviation Codes. Available at https://www.fda.gov/media/107935/download

5. eCFR :: 21 CFR 606.170 -- Adverse reaction file.



Practice Guidelines

The following practice guidelines have been developed by the Washington Clinical Laboratory Advisory Council. They can be accessed at the Medical Test Site Program website.

- Acute Diarrhea
- Anemia
- ANA
- Bioterrorism Event Management
- Bleeding Disorders
- Chlamydia
- Diabetes
- Group A Strep Pharyngitis
- Group B Streptococcus
- Hepatitis
- HIV
- Infectious Diarrhea
- Intestinal Parasites
- Lipid Screening
- PAP Smear Referral
- Point-of-Care Testing
- PSA
- Rash Illness
- Red Cell Transfusion
- Renal Disease
- STD
- Thyroid
- Tuberculosis
- Urinalysis
- Wellness

2024 Northwest Medical Laboratory Symposium (NWMLS): October 24-25, 2024 (virtual)

2025 Joint Spring Seminar: April 2025 (virtual)

The Calendar of Events is a list of upcoming conferences, deadlines, and other dates of interest to the clinical laboratory community. If you have events that you would like to have included, please mail them to chuck.talburt@doh.wa.gov. Information must be received at least one month prior to the scheduled event. The editor reserves the right to make final decisions on inclusion in *ELABORATIONS*.

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Washington State Department of Health, 1610 NE 150th St, Shoreline, WA 98155

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