FDA tightens rule, targets transfusion services

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Beginning next month, on May 7, licensed manufacturers, unlicensed registered blood establishments, and *transfusion services* will be required to report biological product deviations to the Food and Drug Administration if such a deviation occurred when the product was under their control and was subsequently distributed. The report must be filed as soon as possible but no later than 45 days from the date of discovery of the possible deviation.

"Biological product deviations," or BPD, formerly known as "errors and accidents," are "events which may affect the safety, purity, or potency of a distributed biological product and which represent either a deviation from current Good Manufacturing Practice (cGMP), applicable regulations, applicable standards, or established specifications, or are unforeseen or unexpected."

Although licensed manufacturers are now required to report to the FDA "errors and accidents in manufacturing that may affect the safety, purity, or potency of a product," (21 Code of Federal Regulations §600.14), transfusion services, to date, have reported such incidents only on a voluntary basis. Expansion of the reporting requirement to include unlicensed registered blood establishments and transfusion services appears to be driven by the FDA's observation that product recalls by unlicensed blood establishments due to biological product deviations in manufacturing are not now being voluntarily reported to the FDA.

The complexities of this new reporting requirement specific to transfusion services are reviewed below.

The new rule at a glance

- Transfusion services must report to the FDA any biological product deviation associated with the manufacturing of blood components if the event occurred while the product was under their control and was then released to a patient.
- Biological product deviation reports must be filed as soon as possible but no later than 45 days from the date of discovery of the possible deviation.
- Biological product deviation reports will be subject to public disclosure under the provisions of the 1966 Freedom of Information Act.

New reporting requirement

The final rule for reporting BPD, published by the FDA in the Nov. 7, 2000 *Federal Register*, is an amendment of a current regulation (21 CFR §600.14) and the introduction of a new regulation (21 CFR §606.171). Code of Federal Regulations §600.14, formerly titled "Reporting of errors," has been replaced by a new regulatory section titled "Reporting of biological product deviations by licensed manufacturers." The manufacturer that holds the biological product license and has control of the product when the deviation occurs must report the biological product deviation under 21 CFR §600.14. Unlicensed registered blood establishments and transfusion services that had control of the product when the deviation occurred must report biological product deviations under the new section 21 CFR §606.171, titled "Reporting of product deviations by licensed manufacturers, unlicensed registered blood establishments and transfusion services."

Transfusion services must report any event and relevant information associated with the manufacturing (including testing, processing, packing, labeling, storage, and distribution) of licensed and unlicensed blood or blood components if the event represents a biological product deviation.

Under this rule, the entity (licensed manufacturers, unlicensed blood establishments, or transfusion services) that has *control* of a product when a deviation occurs is responsible for reporting to the FDA the biological product deviation, but *only* for products that have been distributed or released to patients. Control is defined in the final rule as being responsible "for maintaining the continued safety, purity, and potency of the product and for compliance with applicable product and establishment standards, and for compliance with cGMP."

When a product is distributed, released, or issued, it is no longer under the control of the transfusion service. The FDA elected to require deviation reporting only for released products because such deviations involve blood products that might be transfused to patients. These released products, therefore, present the greatest risk to public health. If a deviation is discovered but the blood product is still under the control of the transfusion service, the service does not need to file a biological product deviation report with the FDA. The transfusion service must, however, investigate and, if necessary, remedy the deviation as required by cGMP regulations that apply to transfusion services (§606.100[c], 21 CFR §606.100[c]).

Again, it is the responsibility of the establishment that has control of a product when a deviation occurs to report a BPD. For example, a hospital transfusion service pools 24 units of cryoprecipitate and then affixes an incorrect, extended expiration date to the pooled product. The product is then issued to a patient. The transfusion service would need to file a biological product deviation report with the FDA for the following reasons:

- The mislabeling of the product with an incorrect expiration date affects the safety, purity, and potency of the product.
- The pooled cryoprecipitate did not meet cGMP and was distributed to the patient.
- The transfusion service had control of the product when the deviation occurred and the product was released to the patient.

Even if the product was *not transfused* to the patient and was returned to the transfusion service and reprocessed and reworked and the date corrected, the transfusion service is still required to report the deviation to the FDA because the product was dis-

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reports. The agency hopes that using BPD codes will streamline the process of analyzing deviation trends and facilitate data analysis.

Transfusion services must categorize a deviation by assigning a specific code to a reportable event when submitting the report to the FDA. (A complete list of codes can be found at www.fda.gov/cber.) Transfusion services, however, should not use the code topics to determine whether to report an event to the FDA. Transfusion services instead should have a process that determines which events are reportable and that is consistent with the regulation "Biological product deviation reporting for blood and plasma establishments."

A biological product deviation report should *not* be used to report fatalities associated with the collection or transfusion of blood products. Fatalities must be reported to the FDA in accordance with 21 CFR §606.170.

Transfusion-associated fatalities may be reported to the FDA Center for Biologics Evaluation and Research 24 hours per day, seven days per week via voice mail: 301-827-6220, e-mail: fatalities2@cber.fda.gov, or fax: 301-827-6748. Transfusing facilities must file a written report within seven days for fatalities (required by 21 CFR §606.170[b]) and send the report to the Center for Biologics Evaluation and Research Director, Office of Compliance and Biologics Quality, Attn: Fatality Program Manager (HFM-650), 1401 Rockville Pike, Rockville, MD 20852-1448.

The most current information about the BPD requirement can be downloaded from the Web at www.fda.gov/cber/biodev/biodev.htm. The Web site offers a copy of the final rule, titled "Deviations in manufacturing; final rule 11/7/2000," the biological product deviation report form, and form instructions. Also available on the site are deviation codes, blood product codes, and nonblood product codes.

If you need additional information or have questions or concerns related to biological product deviation reporting, contact CBER/OCBQ Division of Inspections and Surveillance Program Surveillance Branch at 301-827-6220 or at bp_deviations@cber.fda.gov. □

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