

unforeseeable event that may affect the safety, purity, or potency of a product. In some cases, a biological product deviation reportable under § 606.171 may actually result in an adverse reaction in the transfusion recipient. In many other cases, the biological product deviation may be discovered before the affected products are administered or administration of the product may not result in an adverse reaction.

Although manufacturers of blood and blood components are currently exempt from the safety reporting requirements under § 600.80, FDA receives reports of fatal adverse reactions related to blood and blood components and may receive some additional information through biological product deviation reporting. However, the agency does not currently receive adequate information to monitor and assess safety-related information concerning the collection and transfusion of blood and blood components. Such information is essential for evaluating the agency's scientific and regulatory policies and for monitoring industry practices and their implications on blood safety. For these purposes, FDA is proposing to amend § 606.170 to require the reporting of all serious SARs, in addition to fatalities, that are related to the collection or transfusion of blood and blood components (*e.g.*, red blood cells, plasma, platelets, and cryoprecipitate). For fatal SARs, proposed § 606.170(c) would continue the current requirement that a fatal SAR be reported immediately by telephone, facsimile, express mail, or electronically transmitted mail and in a written report within 7 calendar days of the fatality. Because blood establishments are already required to investigate all complaints of an adverse reaction related to the collection and transfusion of blood and blood components and many of these reactions are well recognized and understood by blood establishments and by FDA, the agency is not proposing to require the submission of postmarketing periodic safety reports (*i.e.*, TPSRs, PSURs, IPSRs and individual case safety reports—semiannual submissions).

Specifically, FDA is proposing to amend § 606.170 by revising the title of the section to read "Suspected adverse reaction investigation and reporting"; by making editorial changes to § 606.170(a), which prescribes requirements for the investigation and recording of any complaint of an SAR related to the collection or transfusion of blood or blood components; by adding a new requirement for reporting of serious SARs related to transfusion or collection procedures (proposed

§ 606.170(b)); and by redesignating current § 606.170(b) as § 606.170(c) and revising the paragraph as discussed below. FDA is also proposing that the terms "SAR" and "serious SAR," as used in proposed § 606.170, have the same meaning as defined in proposed § 600.80(a) (see sections III.A.1 and III.A.3 of this document).

In general, FDA believes that any SAR related to blood donation or transfusion that requires immediate medical intervention or followup medical attention should be reported. For the purpose of reporting serious SARs related to blood collection, FDA interprets the term to include:

- Vasovagal reactions with syncope (hypotension and bradycardia) requiring medical intervention;
- Citrate reactions requiring significant medical intervention;
- Anaphylaxis or any major allergic reactions;
- Seizure of any type or duration;
- Cerebrovascular accidents;
- Cardiac arrhythmia, angina of any duration, myocardial infarction, or cardiac arrest;
- Clinically significant hypotension;
- Bronchospasm, respiratory insufficiency;
- Arterial puncture, air embolus;
- Phlebotomy-related nerve damage; and,
- Thrombophlebitis, phlebitis, or any procedure-related infection.

For SARs related to donation, FDA interprets the term "serious SAR" not to include:

- Self-limited vasovagal reactions (hemodynamically stable);
- Self-limited citrate reactions;
- Localized hematoma, uncomplicated; and,
- Localized skin irritation, uncomplicated.

For the purposes of reporting serious SARs related to receipt of a blood transfusion, FDA interprets the term to include:

- Any complication from the use of an unsuitable unit, including infusion of hemolyzed blood;
- Any complication from improper blood administration, including failure to use a standard blood filter (*e.g.*, air embolism);
- Induced hemolysis, acute or delayed;
- Transmitted infections, including bacterial infections;
- Associated graft versus host disease;
- Related hypersensitivity with respiratory insufficiency and/or hypotension (*e.g.*, anaphylaxis);
- Transfusion-related acute lung injury (TRALI);

- Induced alloimmunization which prevents effective transfusion therapy (*e.g.*, posttransfusion purpura);
- Induced congestive heart failure; and

- Induced cardiac arrhythmias, including those resulting from metabolic imbalance.

For SARs related to receipt of a blood transfusion, FDA interprets the term "SAR" not to include:

- Febrile nonhemolytic transfusion reactions;
- Related hypersensitivity without respiratory insufficiency nor hypotension;
- Induced alloimmunization which does not prevent effective transfusion therapy;
- Infections not clinically significant to the recipient, such as cytomegalovirus (CMV) infection in an immunocompetent adult; and,
- Induced hemochromatosis.

FDA is proposing to require that for a serious SAR related to blood collection, the establishment performing the blood collection be responsible for reporting the serious SAR to FDA, and for a serious SAR related to transfusion, the establishment responsible for the compatibility testing be responsible for reporting the serious SAR to FDA (proposed § 606.170(b)). FDA is proposing to require that reports of serious SARs, including fatal SARs under proposed § 606.170(c), be reported to FDA using the reporting format described in proposed § 600.80(c)(4). Thus the reporting facility would be required to submit a report for each individual patient on FDA Form 3500A or a computer-generated facsimile of FDA Form 3500A using the appropriate "preferred term" in the latest version of MedDRA (see section III.F of this document).

Current § 606.171 requires reports of biological product deviations be submitted as soon as possible, but not to exceed 45 calendar days. Because there will be instances when an SAR occurs and a biological product deviation may have contributed to an SAR, FDA is proposing to require reporting of serious SARs to the agency within 45 calendar days (for fatal SARs, within 7 calendar days) of the determination that a serious SAR related to blood collection or transfusion has occurred. This will permit a blood establishment to investigate and report both a biological product deviation and an SAR related to the biological product deviation at the same time and will limit the reporting burden. In the case of a reported serious SAR that subsequently results in a fatality, FDA would not require two separate reports,