

the medication error (e.g., patient experienced a seizure). This information is not sufficient for FDA to identify medication errors that could be avoided in the future. For cases that involve a medication error, the safety report needs to be identified as a suspected medication error so that the report can be appropriately analyzed and addressed. FDA concludes that an explicit requirement for reporting medication errors by companies subject to the agency's postmarketing safety reporting regulations is needed to adequately assess and respond to the problem.

FDA is therefore proposing to require that these companies submit to the agency expeditiously all domestic reports of actual and potential medication errors (see section III.D.5 of this document). FDA would review information about suspected medication errors to determine an appropriate risk management plan (e.g., changes to the proprietary name, labels, labeling or packaging of the drug or biological product or educational initiatives to protect public health). This proposal, which is consistent with one of the Department of Health and Human Services' major health initiatives, would allow FDA to form the framework for building a comprehensive risk assessment and management system for preventable SADRs. This proposal is also responsive to the 1999 IOM report, which states that "the Food and Drug Administration (FDA) should increase attention to the safe use of drugs in both pre- and postmarketing process" by "establishing appropriate responses to problems identified through postmarketing surveillance, especially for concerns that are perceived to require immediate response to protect the safety of patients."

II.B.3.b. *Unexpected SADRs with unknown outcome.* FDA is also proposing to require that companies subject to the agency's postmarketing safety reporting regulations submit to FDA in an expedited report SADRs that are unexpected and for which a determination of serious or nonserious cannot be made (*i.e.*, SADR with unknown outcome) (see section III.D.3 of this document). This information is currently submitted to FDA, but, in most cases, not in an expedited manner. A company that receives a report of an adverse drug experience is able, in most cases, to determine if it is serious or nonserious (*i.e.*, whether it meets the regulatory definition of serious), but in some cases, this may not be possible. Currently, most companies that are not able to make this determination designate the adverse drug experience

as nonserious and include it in their next quarterly or annual postmarketing periodic safety report. In some of these cases, the adverse drug experience is, in fact, serious even though the company was not able to make this determination. FDA needs to receive reports of SADRs with unknown outcome expeditiously if the SADR is unexpected so that the agency can evaluate the report in light of other data and information available to FDA to attempt to determine if the SADR is serious. FDA would do this by comparing information on the unexpected SADR with unknown outcome with information on other similar unexpected SADRs with a known serious outcome that are on file with the agency.

II.B.3.c. *Always expedited reports.* FDA is also proposing that companies subject to the agency's postmarketing safety reporting regulations always submit to FDA in an expedited report certain SADRs, which may jeopardize the patient or subject and/or require medical or surgical intervention to treat the patient or subject (e.g., ventricular fibrillation, liver necrosis, transmission of an infectious agent by an approved product) (see section III.D.4 of this document). Currently, all of these adverse drug experiences are submitted to the agency for review, but only some of them are submitted in an expedited safety report (*i.e.*, if the adverse drug experience is serious and unexpected). FDA is proposing that all of them be submitted expeditiously whether the SADR is unexpected or expected and whether or not the SADR leads to a serious outcome. This is because of the medical gravity of these SADRs. For example, even though the labeling for a product indicates that ventricular fibrillation may be associated with use of the product and thus not subject to expedited reporting to FDA (*i.e.*, SADR is expected), the agency needs to review each new report of ventricular fibrillation for this product as quickly as possible to ascertain if there is a qualitative or quantitative change in the nature of the SADR. Information from these reports could result in either new studies being undertaken to evaluate the SADR or appropriate regulatory action by FDA (e.g., labeling change, distribution of Dear Health Care Professional letter, restriction on distribution of product, withdrawal of product from the market).

II.B.3.d. *Blood and blood component safety reports.* With regard to blood and blood components (e.g., red blood cells, plasma, platelets, cryoprecipitated AHF), FDA is proposing that blood establishments submit reports to the agency for all serious SADRs associated

with blood collection and transfusion, in addition to their current requirement at § 606.170(b) (21 CFR 606.170(b)) to submit reports of fatalities (see section III.D.12 of this document). This proposed safety reporting requirement would not impose significant new burdens on blood establishments. This is because under § 606.170(a) (21 CFR 606.170(a)) blood collection and transfusion facilities are currently required to conduct investigations and prepare and maintain reports of all adverse events associated either with the collection or transfusion of blood or blood components. The proposal would simply require that reports of serious SADRs that are currently maintained by the facility, be submitted to the agency within 45 calendar days of occurrence rather than only having these reports be reviewed by FDA at the time of an inspection. Thus, not all serious SADRs are reported to FDA for blood and blood components. FDA believes that it is critical that we receive all such reports to enhance donor safety and also to ensure the safety, purity and potency of blood and blood components for administration to patients.

In the past, the agency has received some voluntary reports that have helped to identify errors in manufacturing and defects in products used to collect blood. For example, in 1997, FDA received reports from a blood establishment of allergic adverse reactions to red blood cells that had been leukoreduced using a bedside filtration method in hematology or oncology patients receiving multiple transfusions. The reactions were related to several lots of Hemosure Leukonet filters. The symptoms included bilateral conjunctival edema, severe headaches, eye pain, nausea sometimes associated with vomiting and joint pain. After investigation and analysis of the reports by FDA, the manufacturer discontinued production of the filter. Voluntary reporting of the adverse reactions by the blood establishment brought the issue to the attention of FDA. However, the time to resolution may have been shortened had these been required to be reported to FDA from all blood centers.

With regard to the safety of donors, FDA review of adverse event reports is important and has resulted in detection and correction of problematic collection procedures. During an inspection, FDA field officers identified a blood collection center that had numerous donors with vasovagal reactions that required treatment by emergency medical personnel. In some of these cases, the donors had to be transported to a hospital emergency room for treatment. Upon investigation, FDA