

DEPARTMENT OF HEALTH AND HUMAN SERVICES**Food and Drug Administration****21 CFR Part 600**

[Docket No. 98N-0815]

Plasma Derivatives and Other Blood-Derived Products; Requirements for Tracking and Notification**AGENCY:** Food and Drug Administration, HHS.**ACTION:** Advance notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is announcing its intention to propose regulations requiring that certain blood-derived products, including certain plasma derivatives, be tracked from a U.S. licensed manufacturer, through the distribution network, to any patient having custody of the product. Additionally, FDA intends to require notification of consignees and patients having custody of a blood-derived product or an analogous recombinant product in the event the product is associated with a potential increased risk of transmitting a communicable disease, as determined by FDA or by a U.S. licensed manufacturer. The regulations would also apply to any blood-derived product which, in the future, may be routinely dispensed to the patient and held by the patient prior to administration. FDA intends to take this action to help ensure notification of patients having custody of blood-derived products when such products may be associated with a potential increased risk of transmitting a communicable disease so that patients may make informed, appropriate decisions. FDA is soliciting comments and information from interested persons concerning the subject matter of the proposed regulations.

DATES: Submit written comments by November 17, 1999.**ADDRESSES:** Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.**FOR FURTHER INFORMATION CONTACT:** Steven F. Falter, Center for Biologics Evaluation and Research (HFM-17), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448, 301-827-6210.**SUPPLEMENTARY INFORMATION:****I. Background**

In a July 25, 1996, report entitled "Protecting the Nation's Blood Supply

from Infectious Agents: the Need for New Standards to Meet New Threats," the United States House of Representatives Committee on Government Reform and Oversight provided recommendations to FDA on improvement of the biologics regulations. One of the recommendations concerned the need for the development of a more effective system to notify patients when there are adverse events associated with blood products.

In response to this recommendation, FDA, industry, and patient groups have already taken a number of actions to improve the agency's and industry's response to situations related to concerns about the safety of blood products. FDA has improved its procedures for planning, monitoring, coordinating, and directing FDA investigations for a range of situations including error and accident reports, recalls, and reports of injury or illness, including those related to plasma derivatives. Although primary responsibility for notification of recalls falls to the manufacturer of the product being recalled, FDA uses a variety of electronic communications to make information on recalls and withdrawals available to the public. These include information on the Center for Biologics Evaluation and Research World Wide Web home page, a Fax-on-Demand system, press releases, talk papers (FDA briefing documents), and a "Blood and Plasma Products" hotline. Interested persons may subscribe electronically to the notification system to receive new information automatically. FDA routinely communicates information regarding recalls and withdrawals of plasma derivatives to consumer groups such as the National Hemophilia Foundation and the Committee of Ten Thousand. FDA continues to work with regulated industry to improve the safety of the blood supply, including the development of new, safer products.

FDA has had extensive dialogue with a variety of interested persons in evaluating the current procedures for identifying and notifying recipients in case of safety issues related to blood products. FDA, along with other Government organizations, held a public workshop on November 19, 1996, to obtain public input on notification of the public on recalls and ongoing investigations (see the notice of meeting in the **Federal Register** of November 1, 1996 (61 FR 56549)). Subsequently, FDA has met with numerous consumer groups and industry organizations to discuss notification issues. After extensive discussions with patient communities and within the

Department of Health and Human Services, FDA believes that there is a consensus that persons in custody of a product that may be associated with a potential increased risk of transmitting disease should be so notified; however, it remains unclear as to what specifically would be the most efficient, least burdensome, process that would ensure appropriate notification of all affected persons.

The voluntary programs for notifying recipients in cases of issues related to the quality of blood products are fairly new and efforts continue to recruit participation by patients who are blood product recipients. Thus the success of the voluntary programs cannot yet be fully assessed. However, the success of such voluntary programs will always depend on the continued voluntary support by manufacturers of blood products and the continued vigorous recruitment of patient/recipients to encourage full participation. FDA is concerned that the continued success of patient notification cannot be assured without regulatory standards for the performance of such notification programs and without a clear mechanism of enforcement in the event a notification program is found deficient. FDA intends to continue to monitor progress in the implementation of the voluntary systems and will consider elements of the voluntary systems when developing any regulations resulting from this notice. FDA believes there should be a standardized notification system, clearly understood by industry and by users of blood products, and over which FDA has clear enforcement authority to help ensure that notification consistently and comprehensively takes place.

Accordingly, FDA is considering rulemaking to provide for the prompt notification of patients who may possess certain plasma derivative products for their own use when information indicates a potential for the product to transmit a communicable disease. FDA recognizes that there are several alternatives as to how this notification could best be accomplished. Any such rule would involve the cooperation of a number of entities who must provide information to help ensure that appropriate notification takes place, including the manufacturers of such products, consignees who hold the product for further sale (wholesale distributors), consignees, such as hospitals and pharmacies, who provide the product directly to the patient, and patients. Accordingly, in sections II. and III. of this document FDA outlines the concepts and alternatives it is considering in the development of these

regulations and invites information and comments on the various concepts and alternatives from all interested persons.

II. General Overview of the Regulatory Plan

Under the biologics licensing and quarantine provisions of the Public Health Service Act (42 U.S.C. 262–264) and the drug, device, and general administrative provisions of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 351–353, 355–360, and 371–374), FDA has the authority to issue regulations designed to protect the public from unsafe or ineffective biological products and to issue regulations necessary to prevent the transmission of communicable diseases. Biological products derived from human plasma have an inherent, potential risk to transmit communicable diseases. Donors of the plasma source material are screened and tested for the potential to transmit a communicable disease. Products made from plasma may be further tested and treated by a process intended to remove or destroy infectious disease agents. However, despite these multiple precautions, there are occasions when problems are identified which may increase the potential risk that the plasma derivative may transmit a communicable disease. Depending on the particular facts, the manufacturer may initiate a recall or market withdrawal of the product so that consignees of the plasma derivative may take appropriate action to prevent the further marketing of the product (see Title 21 of the Code of Federal Regulations (CFR), part 7 (21 CFR part 7) for additional information on the recall and market withdrawal processes).

For some plasma products, generally those that may be chronically administered through the lifetime of the patient, the plasma derivative may be prescribed to the patient and held at the patient's residence until the product is administered. (Note that although FDA is aware only of certain plasma derivative products being routinely held in the patient's custody, FDA intends that any regulations concerning notification would apply to any blood-derived product which may, now or in the future, be released into the custody of a patient.) FDA believes that patients having custody of plasma derivatives are not consistently notified of lot-specific product recalls or withdrawals associated with a potential increased risk of a communicable disease or such notification has not been timely to ensure that appropriate action may be taken by the patient.

There are voluntary tracking and notification systems in place for specific plasma derivatives, but these systems require patients to register with the data base administrator in order for the patients to be notified. In order to protect patients and to better prevent the transmission of communicable diseases through plasma derivatives, FDA is considering the issuance of a proposed rulemaking that would require that patients having custody of plasma derivatives be promptly notified of specific lots associated with a potential increased risk of a communicable disease. Because of the importance of such a notification, FDA is considering defining when notification should take place and setting timeframes during which notification must be performed. The proposed rulemaking would also include requirements for tracking of plasma derivatives to patients who have custody of these products for the purpose of permitting identification of such patients for notifying them of recalls and market withdrawals.

III. Concepts of the Proposed Rulemaking

The following discussion is not intended to indicate the specific content of the proposed rulemaking. It is meant only to describe concepts to be covered by the proposed regulations. The discussion identifies a number of specific topics on which the agency is seeking additional information. However, FDA welcomes comments on any aspect regarding the notification of patients relating to the safety of plasma derivative products. Comments received in response to this advance notice of proposed rulemaking (ANPRM) will be used to develop the proposed rule. FDA specifically requests comments on the concepts that follow.

A. Scope of the Regulations—Types of Blood-Derived Products

The intent of the regulations would be to help ensure that patients possessing plasma derivative products are notified of a potential increased risk of communicable disease so that they may take appropriate action, such as returning the product to the distributing establishment. Therefore, FDA intends to limit the scope of the regulations to those plasma derivatives that may be distributed directly to a patient. Such products include Antihemophilic Factor (AHF or Factor VIII) for the treatment of hemophilia A, Factor IX, used for the treatment of hemophilia B, Alpha-1-Proteinase Inhibitor (Human), used for the treatment of alpha-1 antitrypsin deficiency and products analogous to those listed previously, such as porcine

AHF and products made using recombinant technology. The proposed rulemaking would not apply to plasma derivative products, such as albumin, that are not routinely prescribed for home use.

FDA notes that occasionally patients may take custody of Immune Globulin Intravenous (Human) (also known as IGIV) for administration at home. FDA estimates that approximately 5 percent of the IGIV prescribed is taken into the custody of the patient. FDA believes that such patients should be notified in cases when the IGIV is associated with a potential increased risk of transmitting a communicable disease. The agency also recognizes the complexity, expense, and inefficiency of a system which would be needed to track large volumes of product, for the purpose of potentially notifying a small proportion of patients. It may be more efficient to provide specific arrangements for notification at the time the product is prescribed to the limited number of patients who are taking custody of the product for home use. FDA invites comments and recommendations on how appropriate information regarding product safety can be provided to such patients and whether alternative procedures for such a system should be codified as part of the notification rulemaking. FDA also invites comments as to whether other blood products should be included under the regulations, including a discussion of the extent of the increased burdens and public health advantages associated with such an expansion.

Currently, FDA is aware only of plasma derivative products being released into the custody of patients. It is possible that in the future other products, derived from other blood components, such as red blood cells or white blood cells, may be routinely dispensed into the custody of patients. In such a case, FDA intends that the requirements for tracking and notification would also apply to the blood-derived product. Because the information that FDA has so far gathered and the information being sought by FDA pertains primarily to plasma derivative products, this ANPRM will continue to focus upon plasma derivative products. However, FDA invites comments on what additional blood-derived products may be dispensed into the custody of a patient in the future.

As discussed earlier in this document, a number of voluntary efforts are under way to assist in the notification of persons in custody of a plasma derivative product associated with a potential increased risk of transmitting

a communicable disease. Although FDA believes that there may be innate limitations to any voluntary system, little information is available to the agency regarding the effectiveness of the voluntary systems in place. FDA requests data on the effectiveness of such systems in identifying all persons who may have custody of a plasma derivative product and notifying them in case the product is associated with a potential increased risk of transmitting a communicable disease. FDA also requests comments on whether such systems may be improved and, if so, whether regulations establishing a mandatory notification process would remain appropriate.

B. Scope of the Regulations—Reasons for Notification

At this time, FDA intends that the proposed regulations would require notification only for those plasma derivative lots which, within the dating period of the product, may be associated with a potential increased risk of transmitting a communicable disease. In general, FDA believes that notification of end-users should take place in the same instances for which manufacturers are now either recalling or withdrawing plasma derivative products because of a potential increased risk of transmitting disease. A biological product may be unacceptable for human use due to a wide range of reasons, many not related to communicable disease. FDA is inviting comments on how the basis for notification should be defined in the regulations so as to appropriately establish the criteria for determining when notification should be required. FDA is also inviting comments and information on whether the scope should be expanded to cover other instances, which may affect the safety of the product but which may not be associated with a potential increased risk of communicable disease. An established tracking and notification system could be used in the notification of patients having custody of plasma derivatives for all recalls and market withdrawals. FDA invites comments on the adequacy of the current recall process in situations, other than those related to the risk of communicable disease, and the additional benefits that would be provided by requiring patient notification when compared with the additional burdens associated with the notification process.

C. Who Should Be Responsible for Notification and Related Tracking Responsibilities?

In a recall, the manufacturer has primary responsibility for ensuring that

the recall is undertaken promptly and that, based on an assessment of the risk, it extends to an appropriate level, such as to the end-user of the product. However, other persons, such as the consignees in receipt of the product, play an integral part in the recall process.

FDA is aware of consumer concerns that manufacturers should not know the identity of a patient using its product. Because of concerns about maintaining confidentiality of patients, FDA believes that the manufacturer should not be required to directly contact patients for notification purposes. Such notification could either be accomplished by those consignees who provided the product to the patient or by an independent third party contracted by the manufacturer to notify patients in the case of a notification or withdrawal related to the potential transmission of a communicable disease, while not divulging patient information to the manufacturer. FDA invites comments as to whether the consignees should be held responsible for notification, whether a manufacturer should be required to contract with a third party to perform notification, or whether either option should be permitted under the regulations.

D. Tracking of the Consignment of Applicable Plasma Derivatives

FDA intends that the proposed rule would require that plasma derivatives prescribed to patients for home use be tracked from the manufacturer, to any consignees, and ultimately to such patients for the purpose of permitting identification of such patients when they need to be notified about a product associated with the potential increased risk of transmitting a communicable disease. The tracking of product to intermediate consignees would be necessary for notifying them about the product risk and thus preventing further distribution of the implicated product lot to patients for home use. Depending on the mechanism of notification (see section III.G of this document), required tracking information could be specific for each lot or could simply be the ability to identify all consignees and patients who have received that specific plasma derivative product, regardless of what product lots they may have received. FDA invites comments, data, and other information on the potential recordkeeping burdens that would be associated with tracking such plasma derivative products, including any estimates of the time it would take to prepare such records and of the number of recordkeeping entries that would be necessary each year to maintain these

tracking records. Data are requested both for keeping lot specific tracking information and for product specific information.

E. Initiation of Notification

In most cases the manufacturer would be the first to determine that a plasma derivative may be associated with a potential increased risk of transmitting a communicable disease. However, based, for example, on consumer complaints, laboratory evidence, or information obtained during inspection by FDA or from other public health agencies, FDA anticipates there would be occasions when it is FDA that makes the initial determination that notification is required. In such cases, FDA believes the most efficient means of initiating notification would be for FDA to inform the manufacturer by an appropriate means of rapid communication, such as fax, electronic mail, or telephone, to initiate notification, immediately followed by written information further documenting why the agency deems notification necessary. The previous description is a simplification of the process which would generally take place when problems are perceived with a product. In most cases, there would be considerable discussion among experts, at FDA and at the manufacturer, to evaluate the available information and assess its implications for the safety of the affected products before a decision to notify would be made. Thus, the process described previously would only be the final step in the determination that notification is required.

FDA requests comments on what should be the required elements of the determination that mandatory notification is to take place and what information regarding that determination should be shared between FDA and the manufacturer.

F. Timing for Notification

Because the plasma derivatives held by a patient may be administered at any time, FDA believes that notification of the patient should take place as rapidly as possible after the determination that a notification is necessary. In some cases the first attempt at notifying a patient may not be fruitful; the patient may be away from his or her home or otherwise unavailable. Accordingly, FDA is also considering a regulatory standard for the time by which full notification of patients should be completed (or by when it is determined that the patient cannot be notified with the currently available information). From the time that either the

manufacturer determines notification is appropriate or FDA informs the manufacturer that notification is required, FDA is considering a standard that the initial attempt to notify all persons with custody of the product must take place within 2 days. For those cases when the initial notification attempt fails, FDA is considering requirements that procedures must be in place for two additional attempts for notification; with the final attempt in written form taking place within 1 week from the beginning of the notification process. FDA invites comments and information on how rapidly it is feasible to attempt to contact patients who may possess the product subject to notification and how much time should be allotted to complete the notification process. If possible, the comments should describe in detail the steps which should take place in the notification process and the time which should be allotted for each step. FDA also invites comments on how much time should be permitted to contact consignees, other than the patients with custody of the product, who also may be in possession of the product.

G. Who Should Be Notified

FDA's public health objectives would be met if only those patients are notified who possess the product lot(s) with an increased potential for transmitting a communicable disease. However, a possible alternative would be to notify all patients who have been dispensed the brand of plasma derivative in question during the time period that the product lot subject to the notification has been in distribution. This method would negate the need to track plasma derivative products to the end-user by lot number. FDA invites comments on the comparative advantages and disadvantages of notifying only those patients who may possess the product lot in question versus notifying all patients who may possess the indicated brand of the plasma derivative. Under any system, the information provided to patients would be lot specific.

H. Information Included in a Notification of Patients

Required information to include in a notification of patients could include specific lot information, a statement to describe the risk potentially affecting the product lot, and instructions for further action to be taken by the patients

who have custody of the product lot in question. FDA invites comments on whether the previous information is appropriate and adequately comprehensive for notification.

I. Adequacy of the Notification Process; Quality Assurance

FDA recognizes that, even with a standard mandatory process, notification of every patient may not be successful. For example, the patient may have moved or may be away from his or her home for an extended period of time. FDA is considering a requirement that the manufacturer have a process in place to evaluate, in cooperation with its consignees or any third party involved in notification, the effectiveness of its notification process, such as through the selected sampling of patients who should have been notified, and, with such information, determine how its notification process could be improved. FDA invites comments on the most appropriate means for evaluating the effectiveness of the notification process and who (the manufacturer, consignees, a third party) should be involved in such an evaluation.

J. Relationship of Notification With Product Recalls and Withdrawals

In most, if not all, situations for which FDA is considering requiring notification, manufacturers, under current procedures, would subject the product to recall or market withdrawal. Procedures for product recalls are presented as guidance in 21 CFR part 7. "Market withdrawal" is defined in § 7.3. Product recalls and market withdrawals are similar functions for the removal or correction of a marketed product. In the case of recalls the product is considered to be in violation of the law and may be subject to a regulatory action by FDA, such as seizure of the product. A market withdrawal may be performed for a distributed product associated with a minor violation or for products that are not in violation of the law. Many of the procedures described in this ANPRM as potentially appropriate for the notification process are identical or similar to procedures generally performed in a product recall or market withdrawal (see, for example, the procedures for development of a recall strategy (§ 7.42(a)(1)), conducting effectiveness checks (§ 7.42(b)(3)), and recall communications (§ 7.49)). FDA invites comments on the

interrelationship among product recalls, withdrawals, and the notification process described in this ANPRM. What recall/withdrawal procedures would continue to be appropriate in the event FDA requires patient notification? How may the process best be integrated to ensure effective notification and product removal?

K. Informing Patients of the Notification Process

FDA believes that a patient taking custody of a plasma derivative should be informed that she or he will be notified in the event the plasma derivative is associated with a potential increased risk of transmitting a communicable disease. This information should be provided, in writing, when receiving delivery of the plasma product or before, such as at the time the product is prescribed. FDA invites comments on whether such information can best be provided in the form of patient labeling accompanying the product or should be delivered by other means. FDA also invites comments on whether such information can be standardized for all plasma derivative products and, if so, who should be responsible for preparing such information.

IV. Request for Comments

Interested persons may, on or before November 17, 1999, submit to the Dockets Management Branch (address above) written comments regarding the general and specific issues presented in this ANPRM. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

This ANPRM is issued under section 201 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321 *et seq.*) and under authority of the Commissioner of Food and Drugs.

Dated: June 15, 1999.

Jane E. Henney,

Commissioner of Food and Drugs.

Donna E. Shalala,

Secretary of Health and Human Services.

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