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Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Subject: Comments to the FR Notice of August 19, 1999: Plasma Derivatives and Other Blood-Derived Products: Requirements for Tracking and Notification

To Whom It May Concern:

Novartis Pharmaceuticals Corporation has reviewed the above Federal Register Notice. Specific comments are provided in the attached document.

It is Novartis' position that patient notification should be triggered only in cases of serious adverse health consequences for the patient and should be restricted to those patients having custody of the affected lots of the product.

In order to keep the confidentiality's rights of patients, we believe that the responsibility of notifying the patient should rest with the physician and pharmacist giving the product to patients for home use. This would require appropriate tracking systems in place throughout the distribution chain all the way to the end-user.

Thank you for the opportunity to comment.

Sincerely yours,

Mathias Hukkelhoven, PhD
Vice President, Head
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Attachment

Submitted in duplicate
98N-0815

C4



**Novartis' Comments to the Federal Register Notice of
August 19, 1999: Plasma Derivatives and Other Blood-
Derived Products: Requirements for Tracking and
Notification**

Docket No. 98N-0815

General Comments

Overall comments

Under current regulations and policies, plasma-derived products are treated no differently than other drug products in connection with product recalls. Patients are notified of a recall only when there is a reasonable probability that the use of, or exposure to, a violative product will cause serious adverse health consequence or death (Class I recalls). Based on an assessment of the risk to patients, patient notification can be extended to Class II recalls when use of, or exposure to, a violative product may cause temporary or medically reversible adverse health consequences.

No special tracking requirements are currently in place for Sandoglobulin; in particular, manufacturers/distributors are not required to maintain lot number records of distribution beyond its affected direct accounts. Furthermore, pharmacies and other distributors are not required to maintain logs including lot numbers of product given to particular patients. Currently, therefore, the only feasible way that patients receive notification of a Sandoglobulin recall is by public means. For example, in the past, Novartis has published patient notifications in newspapers or other, similar means. Obviously, this is not a good way to notify only a narrow range of patients.

With this notice, FDA apparently intends to go well beyond these general requirements in connection with patient tracking and notification in the case of certain blood-derived products. The proposed regulation would require tracking of certain blood-derived products to the patient level and notification of consignees and patients having custody of a blood-derived product. This would require the tracking of products from the manufacturer through consignees and ultimately to patients and would require compliance by all parties within the custody chain.

The important point to keep in mind with any patient level notification system is that it may have unintended adverse consequences. In our experience, patients notified of Sandoglobulin recalls become extremely anxious about the situation, and even may avoid taking any of their medication regardless of the lot numbers involved. These risks need to be carefully balanced against the potential threat to patient health which triggers the notice.

As to the standard which should trigger the notice in the first place, we do not understand why we should go beyond the current regulations, requiring patient notification only in cases of serious adverse health consequences or death. Ultimately, we feel very strongly that notification to patients should be as narrowly focused as is consistent with medical need. Specifically with respect to the immune globulins, given the fact that only a small percentage of the product is distributed directly to patients, and the risk of causing undue alarm associated with patient notification, the tracking and notice requirements are clearly too broad if required with respect to all immune globulin patients. We feel that the tracking and notice requirements should focus to those patients taking custody of the immune globulin product.

As to whom should be charged with patient notification, we believe that, because of practical logistical and patient confidentiality concerns, this responsibility should rest with pharmacies and physicians giving the product to patients for home use, and that they

should maintain logs, including lot numbers of the product. Obviously, the manufacturer or distributor would notify the pharmacies and physicians of the recall. This will ensure that the product is tracked to the end user, and will also permit physicians to counsel the patients immediately as necessary.

Definitions

Comments

The draft FR notice requires the notification of patients in the event that product is associated with a potential increased risk of transmitting a communicable disease.

Definition of "communicable" disease would be helpful.

"A potential increased risk" is poorly defined. Specifics of what constitutes a risk should be given. As currently drafted, it seems to refer to a theoretical risk rather than a real risk, in which case patient notification may cause unnecessary and harmful anxiety in patients. We feel that notification to patients should be done when there is a reasonable probability that the use of, or exposure to, the product will cause serious adverse health consequence or death, as established in current regulations. In this case, initial consultation between physicians and patients is essential to provide counseling for patients and avoid a situation of panic.

We can think of one example of a "potential increased risk of transmitting a communicable disease" that currently exists which might warrant patient notification, specifically the case of transmission of nvCJD by a plasma product derived from a donor found to have new variant Creutzfeldt-Jakob disease (nvCJD). The transmissibility of nvCJD by blood or blood products is currently unknown, but it might lead to "serious adverse consequences or death." Therefore, it is reasonable to adopt a precautionary policy of withdrawal of plasma products from donors found to have nvCJD and patient notification of this sort of withdrawal. On the other hand, we would strongly argue against patient notification if plasma product is derived from a donor who has "risk factors" for nvCJD, such as a six months' stay in the United Kingdom from 1980-1996. Without further clarification, this situation might well fall into the proposed "increased risk of transmission" standard.

I. Background

Lines 60-63, Page 2 of 9: 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

Comments

See "General comments and Definition" sections of this document. Furthermore, clarification is sought from FDA between notification as required under "Class I recall communications" and notification due to a potential increased risk of transmitting a communicable disease. We believe that notification to patients should be implemented only in situations when it is warranted from the medical point of view. In these situations,

initial consultation between physicians and patients is essential to provide adequate counseling for patients and avoid any unnecessary anxiety in patients.

II. General Overview of the Regulatory Plan

Lines 42-47, page 3 of 9 states the following: 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.

Comments

As noted above, the patients should not be notified unless the product has a reasonable probability that the use of, or exposure to, the product will cause serious adverse health consequence or death.

III. Concepts of the Proposed Rulemaking

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

Lines 31-35 and 39-42, page 4 of 9: 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 custody of the patient. FDA believes that such patients should be notified in cases....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.

Comments

This would require the tracking of products from the manufacturer through consignees and ultimately to patients and would require compliance by all parties within the custody chain.

It is impossible for the manufacturer and mid-way distributor of the product to identify the 5 percent of the IGIV prescribed patients who take home the product. However, manufacturers and distributors can readily track the product through the distribution network all the way to the pharmacist level and notify the pharmacist about any product recall as well as lots affected by the recall. It then should be the responsibility of the pharmacist to determine whether or not they have received any affected lots of the product and, if so, to notify the patients and patients' physicians of the nature of the recall. This could be accomplished should pharmacies and physicians giving the product to patients for home-care use should maintain logs, including lot numbers of product; thus ensuring that tracking to the end-user would be possible.

B. Scope of the Regulations --Reasons for Notification

Comments

Regarding this section, as noted in our general comments, we believe that manufacturers and distributors alike should not be notifying patients beyond what is established in current regulations (21 CFR. Part 7)

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

Comments

If a mandatory tracking and notification system is imposed, the responsibility of manufacturers and mid-way distributors should extend no further than notifying the pharmacist about any product recall. We currently notify all pharmacists about product recalls and the notification could be extended in the event that product is associated with a potential increased risk of transmitting a communicable disease, such as nvCJD. As already stated above, it then should be the responsibility of the pharmacist to supervise the receipt of any affected lots of the product and notify the patients through their physicians only in the event that the patient has received product from that specific lot.

D. Tracking of the Consignment of Applicable Plasma Derivatives

See comments in section C.

E. Initiation of Notification

Comments

Mandatory notification to patients should be established only in circumstances defined under Class I type of recalls, i.e. when there is a reasonable probability that the use of, or exposure to, a violative product will cause serious adverse health consequences or death. Based on an assessment of the risk to patients, it could be extended to cases when use of, or exposure to, a violative product may cause temporary or medically reversible adverse health consequences (Class II recall). The second scenario should be discussed between manufacturer(s) and FDA in order to determine the risk to patients' health on a case-to-case basis, and then determine whether or not patients should be notified.

Under the scope of the draft notice, mandatory notification could be extended to the case of a plasma product derived from a donor found to have new variant Creutzfeldt-Jakob disease (nvCJD), since there is some probability that the use of the product will transmit nvCJD, which is a serious adverse health consequence.

We strongly believe, however, that patients should not be notified if received plasma product from a donor to have risk factors for nvCJD (e.g. due to six months domicile in the UK from 1980 through 1996), since the harmful psychological stress in patients outweighs the far-fetched risk of transmission of nvCJD.

F. Timing for Notification

Comments

We believe that, when required, notification of patients should take place as rapidly as possible. It is our experience that notification to pharmacists usually takes place within 24 hours of initiating a recall. Subsequently, the pharmacists should make an initial attempt to notify their customers as soon as they are notified about the recall. Pharmacists should be asked about their timing for notification in order to ascertain whether the whole process of notification to patients could take place within 2 days, as suggested by FDA.

G. Who Should Be Notified

Comments

Regardless of the standard triggering a recall, only patients who possess the product lot(s) should be notified.

H. Information Included in A Notification of Patients

The information included in a notification of patients should include:

- Identify the product, size, lot number(s), code(s) or serial number(s) to enable accurate and immediate identification of the product
- Explain concisely the reason for the recall and instruct the patients to discuss the risks and patient follow-up with their physician.
- Provide specific instructions on what should be done with the affected lots of the product.

I. Adequacy of the Notification Process; Quality Assurance

Effectiveness checks are a current requirement for recall. In this particular case, since the responsibility for notification and related tracking would be split between the manufacturer/mid-way distributors (to the pharmacy level) and the pharmacists (to the patient level), we propose that the responsibility for effectiveness checks must also be split accordingly.

J. Relationship of Notification with Product Recalls and Withdrawals

As stated above, the notification process to patients should not go beyond what it is currently established for Type I recalls (extended notification to type II recalls to be determined on a case-to-case basis). However, rather than a public notification, we feel very strongly that notification to patients should be narrowly focused to those having custody of the specific affected lots of the product and only when medically warranted, i.e., those individuals who might suffer serious adverse health consequence as a result of the use of the affected product.

K. Informing Patients of the Notification Process

We do not understand why it is necessary to tell patients, in advance of any problems, when they can be expected to be notified of a recall. It should suffice to form a consensus on when patient notification is necessary and to ensure that patients are notified in accordance with the standard. Notwithstanding the above, the best way to inform patients about the notification standard is in a patient leaflet distributed with the product.

We believe that informing patients of a possible notification in the event that there is a potential and hypothetical risk of transmission of diseases by the product is not medically warranted and will cause unnecessary alarm and anxiety for these patients.

In the particular case of the possible transmission of nvCJD, the best way to proceed is to inform the physician or other qualified personnel responsible for the care of the patient, so that appropriate counseling may be performed at the discretion of the care provider.

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