

Adverse Event Report for an Immune Globulin: FDA Investigation and Actions

SLIDE 1

This presentation will address activities in the Clinical Review Branch and the Division of Hematology, Office of Blood Research and Review, in the Center for Biologics Evaluation and Research.

The Division of Hematology regulates a broad spectrum of products, including immunoglobulins to blood substitutes. This presentation will present an example of how FDA follows up on a reported adverse event, specifically a serious adverse event or SAE, all the actions and investigations undertaken, and where it goes from there. The specific example is for an immunoglobulin product.

SLIDE 2

How does FDA know about a serious adverse event that has occurred after the product is approved? There are various ways, the first one being a MedWatch report. The MedWatch reports are available for all types of products regulated by the FDA: biologics, drugs, devices, cell and tissue-based products, and also special nutritional products and cosmetics. The information on how to report is available on the web page shown in the slide.

Vaccines, however, have a different reporting system called the Vaccines Adverse Event Reporting System, or VAERS. See the web site for VAERS reporting access.

The MedWatch report can be presented to the FDA by the manufacturer of the product itself. The manufacturer comes to know the adverse event from the field – that is, the physicians, investigators, and the manufacturers report it to FDA. Or, the reports can come directly from physicians themselves. It can also be a simple phone call to the FDA information office, or it can be via medical literature reports. Very often, FDA scans through the medical literature reports for cumulative adverse events and takes necessary actions thereof.

SLIDE 3

A serious adverse event is an event that has been associated with death, a life-threatening event, a hospital admission or prolongation of hospitalization, a disability, a congenital anomaly, and an event which requires intervention, whether surgical or medical, to prevent permanent impairment or damage. In most of the cases, these are assessed in relation to the product.

SLIDE 4

Here are some examples of serious adverse events that have been reported to CBER related to IVIG, or intravenous immunoglobulin:

Severe allergic reactions. Most of them are related to a specific lot or lots. In those cases, when that relationship has been found, FDA has recalled, or asked the company to voluntarily recall those lots.

Another event that has been associated with IGIV is renal failure. In order to minimize the risk, FDA has introduced a black-box warning on all the labels of IGIV, alerting the physicians to the association of sucrose in IGIV and renal failure. In addition, the risks of renal failure associated with IGIV were published in MMWR, the morbidity and mortality weekly reports article published by the CDC.

A relatively recent report related with IGIV and included in the black-box warning is the blood glucose monitoring interferences by the IGIV products, specifically those which have maltose in the formulation. This has led to package insert revisions, and to an FDA event posting in the form of a Dear-Health-Care-Provider letter, alerting the physicians of this interference.

Intravascular hemolysis associated with Anti-D product WinRho has also led to a package insert revision in the warnings and precautions section, as well as a "Dear Health Care Provider Letter" posted on the FDA web page.

SLIDE 5

Let's discuss the actions or investigations which follow when the report is received by the FDA. To decide whether this is really a serious adverse event or not, FDA tries to gather all the detailed medical information as early and as soon as possible. Decisions are made whether an immediate action is indicated for patient safety -- in other words, whether FDA has to issue a recall of that product.

The black-box warning does not happen immediately. It takes time for negotiations that affect the package insert change.

SLIDE 6

The later actions are based on the data received and generated. The first action is to avoid or ameliorate the SAE reported. This can be addressed by:

One, risk communications, in the form of an FDA event page, where a Dear-Health-Care-Provider Letter is posted, highlighting the risk, or the adverse event;

Two, by presenting the safety concerns at a public forum, such as Blood Product Advisory Committee presentations; and

Three, by publishing the safety concern. In 2006, FDA published in Transfusion Medicine a report on cumulative safety data on IGIVs. These were collected from

literature reports. That publication also led to the package insert revision of all the IGIVs.

Sometimes, FDA also presents this to the interest groups and professional organizations, for example, the IDF, the Immune Deficiency Foundation. The recall of a specific lot, especially when an allergic reaction was reported, other previous recalls, could be due to the manufacturing deviations. An example is Albuminar and PlasmaPlex, which happened when sepsis was detected due to contamination of the vials. In that case, all the lots were recalled, because there was a manufacturing deviation.

SLIDE 7

For this presentation, the example case study is IVH associated with RhoD when given to ITP patients, or idiopathic thrombocytopenic purpura patients. The CBER Office of Biostatistics and Epidemiology, or OBE, received an email report about hemolysis in a patient who received IGIV for ITP indication. This email was forwarded to the product specialist.

SLIDE 8

Upon receipt of that email, an investigation followed. Once the report was received, CBER called the physician to obtain further information, because the first report did not have all the relevant information.

CBER obtained information on the lot number of the IGIV, clinical details, and the dose that the patient received.

Then CBER called the manufacturer to request the test results for the implicated lot -- in other words, whether the lot had met the specifications for the Anti-A, Anti-B and Anti-D -- and also requested other SAE reports from the implicated lot. OBE was notified, as well as CBER's upper management and the Blood Safety Team.

SLIDE 9

Based on the information now gathered, CBER determined that the hemolysis was temporally associated with the IGIV treatment, and all the laboratory parameters showed evidence of hemolysis.

The lot release tests, which are provided by the manufacturer, showed that all the specifications for Anti-A, B and D were all within specifications. Hemolysis is listed as an adverse event in the IGIV package insert. So, based on this preliminary assessment, CBER concluded that a recall of that lot was not indicated at that point.

SLIDE 10

In the meantime, CBER was gathering additional information from the FDA databases, whether additional cases of hemolysis had been submitted to the

FDA, and whether they were all implicated to the lot which this patient had received. It was found there was no cluster of lot-related cases reported to the manufacturer or to the FDA for this lot.

FDA tested the product in the laboratories for Anti-A, Anti-B and Anti-D, and agreed that it met the specification of what the manufacturer had reported.

Additional information from the patient's medical records was obtained. This patient had received a second investigational antibody product, which may have contained Anti-RBC antibodies. The patient had also received higher doses of IGIV than recommended in the package insert.

SLIDE 11

Further analysis showed that the patient with hemolysis had received two antibody products, but they both were within the specifications. In both cases, the package insert included hemolysis as a possible side effect, but neither product had any other hemolysis reported for the lot used in this patient.

FDA concluded that it is possible the combination of the treatments predisposed this patient to hemolysis, or that the patient had some underlying cause or risk, which could have precipitated this hemolysis.

SLIDE 12

The hemolysis was associated because of the use of the two products in this patient, Product 1 and Product 2.

Remember, Product 2 was an investigational product. So, a recall of the lot was not indicated. FDA and the manufacturers agreed to continue monitoring these specific lots closely for any additional hemolytic event. The warnings and precautions sections in the package insert, highlighting the risk factors which can lead to hemolysis in patients receiving IGIV for ITP indication, was improved.

SLIDE 13

While investigating an SAE obtained post-market, the most important points for assessments are as follows:

One, obtain the lot numbers of the product,

Two, obtain events from that lot, reported to the regulators or to the industry, as they may not always be identical,

Three, obtain information from the manufacturers about the latest test results, or about whether there has been any manufacturing deviations.

Four, verify the patient information. Remember that verification that is verbal, by phone, may be incomplete or miscommunicated, written reports may be

incomplete, and medical records are likely to be most complete, though obtaining medical records could take time.

Fifth, if possible, the product test results are verified.

SLIDE 14

In order to decide upon an action, a team consisting of a group of specialized regulators is formed. An early action is needed to identify the lot and obtain the patient information. FDA obtains as much patient information as possible. This decision may be revisited based on any new information that becomes available during the investigation.

FDA analyzes the root cause of SAE where possible.

SLIDE 15

The team which evaluates the adverse event reports consists of medical reviewers, product reviewers, the epidemiologists and safety evaluators from OBE, and reviewers from the Office of Compliance and Biologics Quality.

SLIDE 16

A CBER initiative to obtain this information quickly, evaluate it, and, if needed, rapidly alert the medical community of any SAE, was the establishment of a Blood Safety Team in 2006.

The goal of this team is to formalize the central operating procedures, to establish roles and responsibilities in the management of blood safety issues, and to enhance internal and external communications as early and efficiently as possible.

SLIDE 17

The objectives of this team are:

To improve the CBER responses to the blood safety issues through defined cross-office collaborations, which creates increased sensitivity to safety signals.

To improve the value of safety information and broaden public and regulated industry access to the information.

To improve the processing of blood safety information through establishment of a forum for review and evaluation, permitting discussions in a non-crisis mode, and facilitating anticipation of events.

And last, but not least, to enhance external outreach evaluation and risk communication.

SLIDE 18

The Blood Safety Team coordinates an investigation and responses for the identified safety issues; coordinates an investigation of potential shortages of blood and blood products which may occur due to some manufacturing changes, due to reports of adverse events, or due to the reports of reduced stability; and then, seeks regulatory pathways to avoid shortages.

SLIDE 19

This slide reviews a few of the acronyms used in this presentation.

Slide 20

This concludes the presentation,
"A Case Study - Adverse Event Report for an Immune Globulin: FDA
Investigation and Actions".

We would like to acknowledge those who contributed to its development. Thank you.