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BLOOD SAFETY

Enhancing Safeguards Would Strengthen the Nation's Blood Supply

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Blood Safety: Enhancing Safeguards Would Strengthen the Nation's Blood Supply

Mr. Chairman and Members of the Subcommittee:

It is a pleasure to be here this morning to discuss our examination of the safety of the nation's blood supply. Donors give approximately 14 million units of whole blood and 12 million units of plasma annually. As many as 4 million patients receive transfusions of whole blood components and millions more receive plasma products each year. Since the human immunodeficiency virus (HIV) was introduced into the U.S. blood supply in the early 1980s, the benefits of a potentially life-saving transfusion have had to be weighed against the risks of acquiring this deadly disease through blood transfusion.

Widespread concern about the safety of the blood supply has led to many positive changes in the way blood is collected, processed, and transfused. In testimony on July 28, 1993, before the Subcommittee on Oversight and Investigations of the House Committee on Energy and Commerce, the Commissioner of the Food and Drug Administration (FDA) outlined five overlapping "layers of safety" that provided a framework for regulating and monitoring the blood supply industry: (1) donor screening, (2) donor deferral registries to list unsuitable donors, (3) viral testing, (4) quarantining blood until tests and control procedures have established its safety, and (5) monitoring facilities and investigating adverse incidents to ensure that deficiencies are corrected.

While the blood supply is very safe, no amount of federal regulation can entirely eliminate blood transfusion risks because of the biological nature of the product itself. Increasingly sophisticated tests are shortening the time between infection and detectability of infection in the blood. Blood donated during this interval, known as the window period, is the leading cause of infected blood remaining in the blood supply.[1] Improved viral tests will continue to close this gap, but the window period is not likely to disappear completely.

My statement today is based on our two reports on the blood supply issued in February 1997.[2] In these reports, we assessed the current risks of transfusion, evaluating the content and quality of data collected to assess these risks. We also evaluated the FDA's layers of safety and their ability to ensure the safety of the nation's blood supply.

[1]The window period is the time from infection to the point at which currently licensed test kits can ascertain antibodies or antigens to certain viruses tested for by blood facilities.

[2]Blood Supply: Transfusion-Associated Risks (GAO/PEMD-97-2, Feb. 25, 1997) and Blood Supply: FDA Oversight and Remaining Issues of Safety (GAO/PEMD-97-1, Feb. 25, 1997).

In summary, our analysis of current risks from transfusion showed that, while the nation's blood supply is safer today than at any time in recent history, some risk remains, even if all the safeguards available work perfectly. We also found several vulnerabilities and gaps in current procedures which, if eliminated, would provide greater assurance of safety for the nation's blood supply. The most serious of these problems follow:

- Not all donors who test positive for certain viruses are notified, which means that they can attempt to donate again and also may go without treatment.
- Similarly, not all recipients of virally contaminated blood are notified, which may keep them from seeking treatment and also allow them to transmit the disease.
- Blood facilities are not required to remove from their inventory blood from donors who have subsequently tested positive for viral infections.
- Unlicensed blood facilities that, together, produce 10 percent of the nation's blood do not have to submit to FDA error and accident reports that may signal the need to recall potentially contaminated units of blood.
- FDA's investigations of error and accident reports that warrant a recall take a long time and increase the risk that units will have been transfused before a recall is accomplished.
- Finally, FDA's inspections of blood facilities are inconsistent in focus, scope, and documentation.

Our reports contained a number of recommendations to the Secretary of Health and Human Services to eliminate these weaknesses in the quality assurance system for the blood supply.

Transfusion-Associated Risks

At this time, I would like to tell you more about our analysis of the current risks of transfusion-associated complications from blood, assuming all layers of safety are working properly—that is, blood from donors who were properly screened, whose names were checked against a deferral registry, whose viral test results were negative, and so on.

In conducting our analysis, we reviewed current data and the scientific literature as well as interviewed government and industry epidemiologists. We then compared our final estimates on risks from blood transfusions with data on risks from other health-related causes. We included risks from eight viruses, various bacteria, one parasite, and four complications

of transfusion itself.[3] When we encountered differing estimates of risks from research that we considered equally valid, we chose the higher estimate.

We found that the blood supply is safer today than at any time in recent history. Nevertheless, blood is a biological product, and some risk remains. Eight of every 10,000 donated units carry some kind of potentially serious risk to the recipient, including allergic reactions, bacteria, reactions to incompatible blood, and viruses. We calculated that 4 of every 1,000 patients who receive the average transfusion of 5 units of blood are at risk of receiving a contaminated unit and thus may be exposed to conditions with the potential for the development of serious (that is, chronic, disabling, or fatal) outcomes at some point in the future. We believe this risk is small considering that as many as 50 percent, or 500, of the 1,000 recipients would be at serious risk of dying immediately if they did not receive transfusions.

Moreover, not all recipients of a contaminated unit acquire the disease it contains. And, many recipients die soon after transfusion from the underlying condition for which the blood was prescribed. Finally, the likelihood that a patient will develop chronic disease or die is small for some diseases that are transmitted by transfusion. We determined that the overall risk of developing chronic disease or dying as a direct result of a blood transfusion is about 4 in 10,000, which translates into about 1,525 of the 4 million patients who receive transfusions each year. Thus, if all the safeguards are working properly, the risks are relatively small and are certainly far outweighed by the benefits.

Because risks should never be discussed out of context, we sought to determine whether these transfusion risks were small or large by comparing them with other known health-related risks. The risks to blood transfusion recipients are considerably smaller than the risk of dying as a direct result of surgery, the risk that a hospital stay will result in death or chronic disability, the risk of suffering a serious injury from hospital drug therapy, and the risk of developing an infection of unknown cause in intensive care.

Risks From Plasma Products

The risk estimates I have just presented are for whole blood products from unpaid donors, which account for about half of all donations. The

[3]The viruses included were hepatitis A, hepatitis B, hepatitis C, HIV-1 and HIV-2, human T-lymphotropic virus type I (HTLV-I) and type II (HTLV-II), and non-ABC hepatitis. The parasite-transmitted disease included was Chagas', and the transfusion complications were ABO incompatibility, acute lung injury, allergic reaction, and circulatory overload.

remaining blood products are plasma products, such as immune globulins or clotting factors, which are usually obtained by commercial facilities from paid donors. Because only limited data are available concerning the risks posed by plasma products, we were unable to include plasma derivatives in our analysis of risks. However, because the ways in which plasma products are manufactured differ from the way whole blood products are prepared, and because these products are used differently, it may be worth highlighting some of these features to try to understand the nature, if not the full extent, of risks associated with this sector of the blood supply.

More than 40 million hospital patients use plasma products each year. Plasma is the liquid portion of blood, containing nutrients, electrolytes (dissolved salts), gases, albumin, clotting factors, hormones, and wastes. Many different components of plasma are used for purposes that range from treating the trauma of burns and surgery to replacing blood elements that are lacking as a result of a disease such as hemophilia.

In the 1980s, before the etiology of HIV transmission was understood, many hemophilia patients used plasma products infected with HIV, and 63 percent of all hemophilia patients in the United States became infected as a result. Many more contracted hepatitis B and hepatitis C. Since the introduction of antibody tests and heat treatments and solvent-detergent washing processes for inactivating and removing viruses, however, the transmission of disease has been considerably reduced.

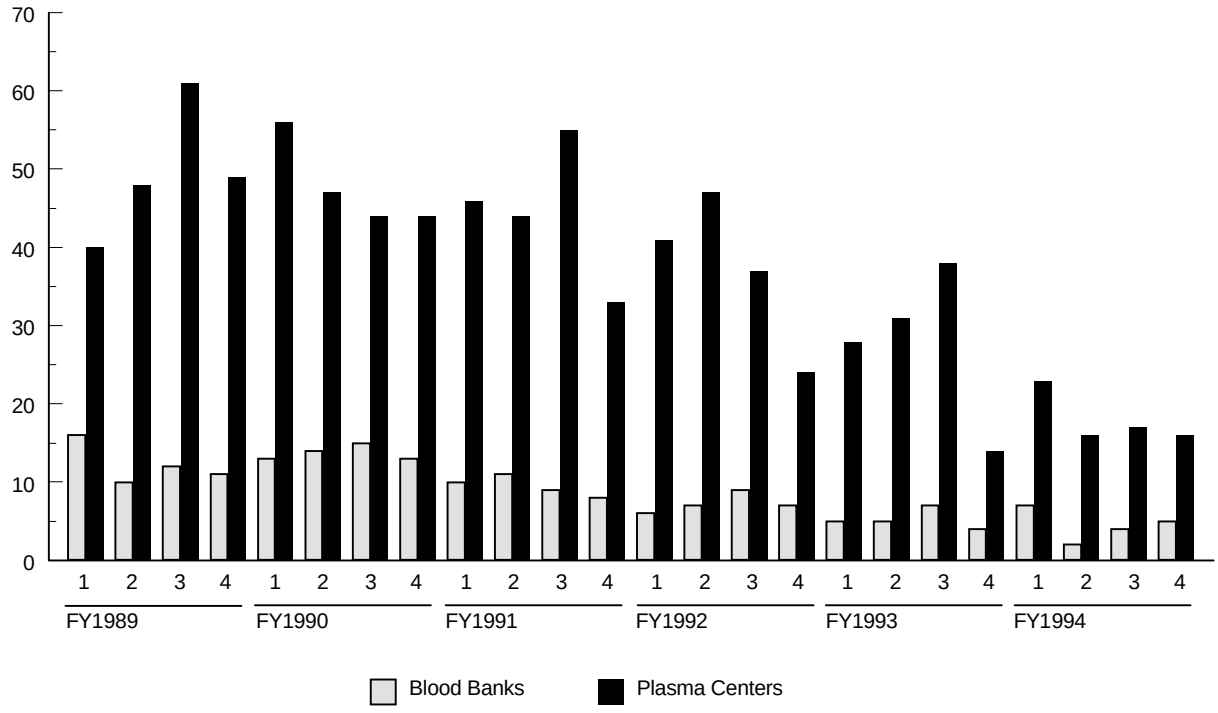
Current techniques appear effective for protecting against the transmission of HIV, hepatitis C, and hepatitis B. But certain viruses that are not surrounded by a fatty envelope—such as hepatitis A and parvovirus—are not inactivated by current techniques. Moreover, different manufacturers producing similar products may or may not use these techniques.[4] The extent to which current manufacturing techniques will be effective against unknown pathogens that could enter the blood supply is not known.

[4]In December 1994, FDA notified manufacturers of immune globulin products that it would begin testing for hepatitis C in all products that had not undergone a validated virus inactivation or removal process. The products affected by this policy include Rho(D) immune globulin for Rh-negative pregnant women and specific immune globulins for hepatitis B; tetanus; and varicella-zoster, the agent that causes chicken pox. No new cases of hepatitis C transmission by these intravenous products have been reported to date. A similar product, immune globulin for intramuscular administration, is not virally inactivated. Although no cases of hepatitis C transmission by intramuscular administration of immune globulin have ever been reported, concerns have been raised about this product, and FDA allows only the manufacturing lots that have been tested for hepatitis C to be distributed. HIV is a delicate virus that is readily inactivated. No cases of HIV transmission by plasma products inactivated according to current standards have been reported.

Despite the evidence that viral inactivation and removal processes improve the safety of plasma products, the fact remains that the paid plasma donor pool has higher rates of viral infectivity than the volunteer whole blood donor pool. Unlike whole blood, plasma is typically collected from paid donors in a commercial setting. In 1978, FDA required that each blood unit be labeled as either volunteer or paid. In the regulations, FDA concluded that paid blood donors were more likely to transmit hepatitis to recipients than were volunteer donors. FDA's conclusions were based on research evidence showing higher rates of hepatitis in commercial donors and in recipients of paid donor blood as well as evidence showing that the elimination of commercial blood resulted in substantially fewer cases of posttransfusion hepatitis. While the commercial donor pool for whole blood is all but nonexistent in the United States today, the plasma industry continues to rely on paid donors to supply the raw plasma for further manufacturing into plasma derivatives.

We were unable to obtain national data on the viral test positivity rates among paid plasma donors compared with those of volunteer blood donors. We did, however, find several sources of information pertaining to this issue. First, we found that California requires the reporting of initial and confirmed HIV prevalence rates for both blood banks and plasma collection centers. Figure 1 shows that the confirmed HIV prevalence rates per 100,000 commercial plasma donations in California have decreased in recent years but remain substantially higher than those same rates for volunteer whole blood donations.

Figure 1: Quarterly Confirmed HIV Prevalence Rates for Donations in California, Fiscal Years 1989-94
Per 100,000 Donations



Note: These rates are reported Western Blot-confirmed HIV prevalence rates per 100,000 commercial plasma donations and volunteer whole blood donations.

Source: California Department of Health Services, Office of AIDS, HIV/AIDS Epidemiology Branch, Sacramento, California, August 1995.

Unlike whole blood donors, who cannot donate blood more often than once every 8 weeks, plasma donors can donate twice a week. As a result, fewer plasma donors are needed to collect 100,000 units. Moreover, several plasma units could be donated during a window period, whereas it is unlikely that more than one whole blood unit could be donated in a window period.

We also analyzed the clinical data that plasma manufacturers submitted to FDA during the approval process for several viral tests. The test-positive rates for commercial plasma donors were substantially higher than those

of volunteer whole blood donors, ranging from about 2 to 20 times higher on the different tests.

While most commercial plasma donors are healthy and free of disease, monetary incentives such as those offered by commercial plasma-collection centers may be tantalizing to some of those who are known to be at risk for infectious diseases, such as intravenous drug users and prostitutes. Screening questions address these risk behaviors, but there is no definitive way to screen out all risky donors, and current tests may not be sufficient to catch all infected units.

Newly emerging and yet unknown viruses often enter the population through high-risk individuals. Viral antibody tests may not yet exist for these new viruses, and current viral inactivation and removal techniques may be ineffective for them. Moreover, one infectious donation can contaminate an entire pool of as many as 60,000 units. Without national data on the differences in prevalence and incidence rates between paid and volunteer donors, it is not possible to draw firm conclusions about potential risks posed by plasma derivatives. Such data would be valuable because they could be used to monitor the blood industry in its entirety.

FDA Oversight and Remaining Issues of Safety

To test whether blood supply safeguards are working, we examined FDA's layers of safety and found vulnerabilities throughout, including problems in the areas of donor screening, notification, postdonation information, recalls, and FDA standards and inspections.[5] These vulnerabilities are summarized in the appendix.

Donor Screening

Donor screening, the first layer of safety, is designed to prevent the donation of blood by people who have known risk factors for disease transmission or are not in good health. High-risk donors, those whose blood may pose a health hazard, are encouraged to exclude themselves. All potential blood donors must answer a series of behavioral and medical questions. If any one answer indicates high risk, the prospective donor is not allowed to donate. If the questions are answered truthfully, they isolate about 90 percent of people whose risk of having HIV is too recent

[5]We limited the scope of our investigation to policies and procedures that were current in 1994. Thus, we did not examine problems and consequent policy changes of the mid-1980s as a result of the discovery that HIV can be transmitted via blood transfusion. Nor did we examine the patterns of violations by individual facilities. The focus of our work was the general policies and procedures in place to help ensure the safety of the blood supply.

for their bodies to have produced sufficient antigen or antibodies that would be detected by viral screening tests.[6]

We found two potential vulnerabilities in the area of donor screening. First, while questioning and screening donors about their behaviors and medical history is important in maintaining a safe blood supply, studies have shown that the style and content of history taking may influence the accuracy and completeness of donor's answers. The American Association of Blood Banks has a comprehensive and readily available uniform donor history questionnaire that, if adopted by more facilities, could strengthen donor screening procedures. Second, the amount of privacy for screening donors varies across blood facilities. A lack of privacy during donor screening inhibits forthright communication.

The importance of screening donors with validated questionnaires in a private environment is underscored by a study published after our reports were issued of 35,000 blood donors who completed a mail survey 4 to 8 weeks after their most recent blood donation.[7] A total of 186 per 10,000 donors (1.9 percent) reported a deferrable risk that was present at the time of their donation, and 39 per 10,000 donors (0.4 percent) reported having engaged in behaviors that should have resulted in deferral within the 3 months prior to donation. Further refinement of the donor qualification process could help deter these potentially risky donors from donating blood.

Notification

At both the deferral and testing layers, blood facilities have an opportunity, and sometimes a requirement, to notify donors as well as recipients of indications of disease. We found two areas of concern related to notification. Not all blood facilities notify donors that they have tested positive on a viral screening test and that they are deferred from donating again.[8] FDA recommends notification of donors deferred for HIV only. While the blood is not used in cases in which test results are positive, this does not ensure that these donors will not attempt to donate at another site;

[6]Antibody tests detect antibodies that the human body produces in its immune response to a virus, whereas antigen tests detect a component of the actual virus. Because it takes time to develop antibodies, antigen tests detect infection earlier than antibody tests.

[7]Alan E. Williams and others, "Estimates of Infectious Disease Risk Factors in U.S. Blood Donors," Journal of the American Medical Association, 277:12 (1997), pp. 967-72.

[8]Screening tests are conducted for hepatitis B by testing for surface antigen (an indication of active virus) and antibody to core (an indication of resolving or past infection and a surrogate marker for high-risk behavior, such as intravenous drug use); for hepatitis C by antibody test; for HIV by antibody and antigen tests; for HTLV-I by antibody test; and for syphilis by serological test. Increasingly sophisticated tests are closing the time between infection and detectability of infection in the blood.

neither does it prompt them to change behaviors or seek treatment so that they do not transmit the disease to family members or others.

Also contributing to this problem is the fact that facilities vary in the extent to which they perform confirmatory or supplementary tests on blood that has repeatedly tested reactive on initial screening assays. FDA only requires confirmatory testing of HIV-positive units. Units repeatedly reactive for other viruses do not always have confirmatory tests performed on them, and confirmatory tests for some viruses have not been developed or licensed by FDA. Thus, facilities that do not perform such tests cannot adequately inform donors about their disease status, even if they notify donors that they are deferred.

Facilities also vary in their policies for notifying recipients who have received blood from donors who later test positive for viruses and for conducting lookback, that is, tracing and removing units from implicated donors that remain in inventory. FDA requires these practices for HIV and recommends—but does not require—quarantine and destruction of units in inventory from donors who subsequently have repeatedly reactive tests for hepatitis B, hepatitis C, and HTLV. FDA has made no recommendations about notifying recipients who may have received blood infected with these other viruses.

Not notifying these recipients poses a potential public health problem. Using hepatitis C as an example, we found that, although the mechanisms of secondary transmission are not well established, some secondary transmission of hepatitis C does occur. The Centers for Disease Control and Prevention has issued guidance for infected people that includes recommending protected sex for individuals with multiple partners and the avoidance of sharing common household articles, such as razors and toothbrushes. Furthermore, abstinence from alcohol is strongly recommended for infected people because alcohol intake results in more liver disease and increases the risk of liver cancer. Although medical therapies are not yet 100-percent effective, clinical trials for alpha interferon therapy show that 23 percent of patients achieved a long-term remission at the end of treatment. We believe recipients of hepatitis C-infected blood should have the right to decide with their physicians whether medical therapy is indicated for their disease. Moreover, should a more effective therapy arrive in the future, recipients who are not notified today would likely be lost to follow-up.

Postdonation Information

Another critical layer of safety is the quarantining of blood for a period of time following donation during which additional information and test results may lead to the decision that the blood is unsuitable for use. For example, donors may provide information after donating that would have excluded them from donating had it been known at the time of donation. Sometimes donors call to report relatively minor issues such as having developed a cold; other times, donors call to say that they engage in behaviors (such as intravenous drug use) that put them at serious risk of disease; still other times, donors report at a subsequent donation attempt that they engage in behaviors that put them at serious risk of disease. If such postdonation information is received after a unit is made available for distribution, the blood facility must submit this information as an error and accident report—a type of report that a facility must file with FDA whenever it discovers a mistake that affects the safety, purity, or potency of blood products. Postdonation information accounted for about 3,800, or more than one-third, of all error and accident reports in fiscal year 1994.

The preponderance of errors and accidents related to postdonation information is a concern. It could indicate that the system is working properly or that FDA should more clearly define what is to be reported. The large proportion of errors and accidents discovered as a result of postdonation information also calls into question the adequacy of screening processes. For example, 65 percent of the error and accident reports related to postdonation information stemmed from information obtained at a subsequent donation.

While we cannot explain the differences, we found far fewer postdonation error reports from plasma centers than from licensed whole blood facilities: Whole blood facilities' reporting rate was 135 times higher, although both collect approximately the same number of units each year. Since data show higher prevalence rates of HIV and perhaps other diseases at plasma centers, as we pointed out earlier, this appears to be an area where more information is warranted.

Recalls

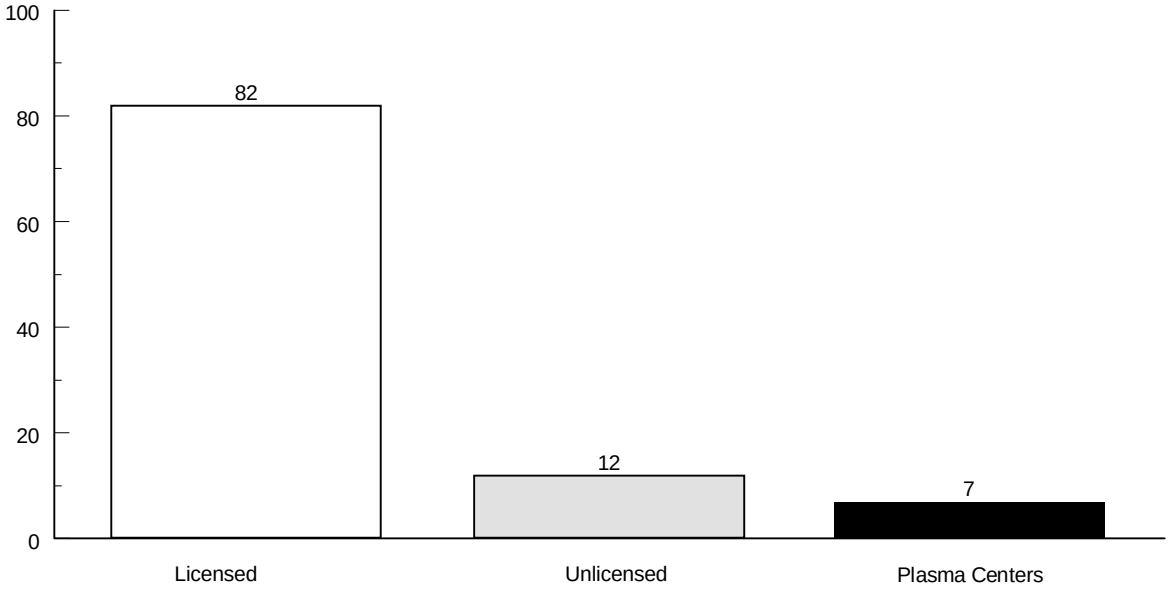
As the final layer of safety, blood facilities are obligated to monitor and investigate errors and accidents in their procedures, to audit their systems, and to correct deficiencies. As explained earlier, if an error or accident results in a potentially contaminated unit of blood being made available for distribution, licensed facilities (both whole blood and plasma) are required to report the incident to FDA. Unlicensed facilities are requested to voluntarily report such incidents.

Once a facility reports an error or accident to FDA's Center for Biologics Evaluation and Research (CBER), depending on the severity of the incident, FDA's district field office located nearest the facility evaluates it and may recommend a recall. Most recalls are initiated by the responsible establishment and often are completed before FDA learns of them. Recalls are voluntary; while FDA may prompt a firm to initiate a recall, this occurs in only 25 percent of recalls. In egregious cases, such as those posing an imminent threat to the public where the blood establishment resists initiating a recall, FDA has the authority to initiate product recalls but has never done so for blood products. CBER's role is to determine that an unsuitable product should be recalled if the establishment has not already done so and to classify the recall based on a health hazard evaluation to establish the level of FDA follow-up required to ensure that the public is protected.

Only licensed facilities are required to submit error and accident reports to FDA. Although unlicensed facilities are asked to voluntarily submit their reports, FDA's annual summaries suggest that unlicensed facilities may be underreporting. Our analysis of FDA's summary for fiscal year 1994 found that unlicensed facilities submit only 12 reports for every 100,000 units of blood they collect, compared with 82 reports per 100,000 units for whole blood facilities (see fig. 2). This means that unlicensed facilities submit only about 1 percent of the reports, although they account for 10 percent of the blood supply. While plasma centers are required to submit error and accident reports, they also report at rates much lower than licensed whole blood facilities, despite collecting equivalent amounts of blood products. Moreover, 39 percent of the error and accident reports that CBER received from plasma centers were sent forward to the districts to be reviewed for potential product recalls, as compared with only 5 percent of reports submitted by licensed whole blood facilities.

Figure 2: Total Error and Accident Reports by Facility Type, Fiscal Year 1994

Per 100,000 Units Collected



Source: GAO's analysis of FDA's Annual Summary for fiscal year 1994.

Unlicensed facilities also submit fewer error and accident reports in situations that end in product recalls. In roughly two-thirds of the recalls in 1994, a report was submitted before the district office's recommendation for recall: Nearly all of these reports came from licensed facilities, including plasma centers.[9] More than 70 percent of licensed facilities submitted a report before recall, but only 17 percent of unlicensed facilities did this. Given that these reports are one way of alerting FDA to the need for an immediate recall, we believe that underreporting by unlicensed facilities is a serious problem.

In those cases in which facilities are reporting, the Department of Health and Human Services' (HHS) Inspector General's Office has found that

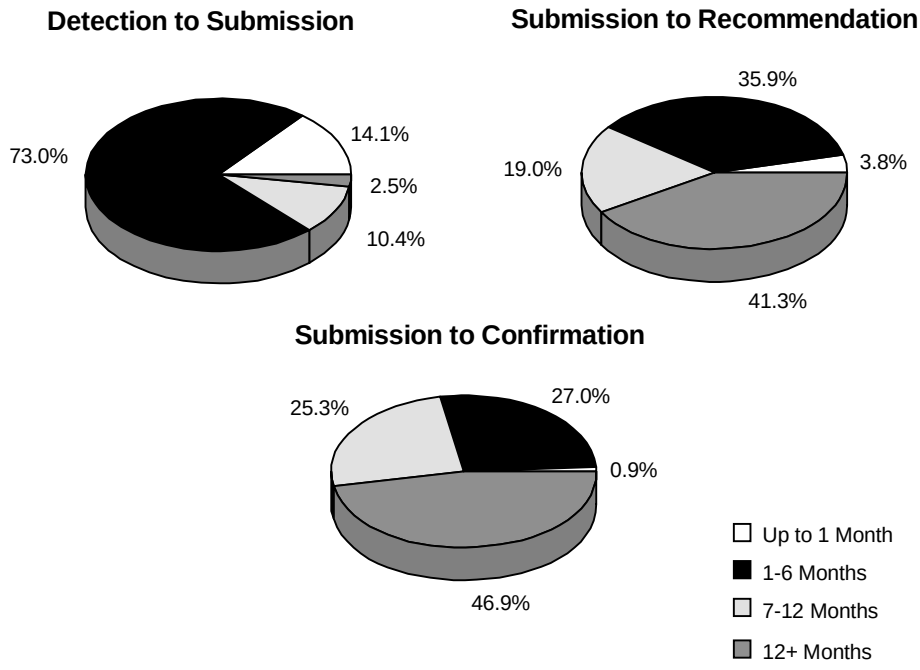
[9]Our statistical analysis determine that this difference between licensed and unlicensed facilities was highly significant ($t = -8.96$, $p < .0001$).

timeliness is a problem.[10] For a random sample of 163 reports from October 1992 to April 1993, the time between the date when a blood facility detected an error or accident and the date when this information was submitted to FDA ranged from less than 1 month to more than 1 year, the average being a little over 4 months. While 14 percent of reports were submitted within 1 month, 13 percent were reported 6 months or more after the error was detected.

Further, we found that timeliness of FDA actions in response to reports is also a problem. Our analysis of FDA's recall database showed that in 60 percent of cases, 7 months or more elapsed between the time of report submission and the district office's recommendation to CBER that a recall should be considered. The average time for CBER review was 9 weeks, but reviews sometimes took as long as a year. The total time from report submission to recall confirmation and public announcement ranged from a little over 1 month to 2-1/2 years, with an average of nearly 9-1/2 months; in 70 percent of cases, the time was 7 months or more (see fig. 3).

[10]Office of Inspector General, HHS, Reporting Process for Blood Establishments to Notify the Food and Drug Administration of Errors and Accidents Affecting Blood, A-03-93-00352 (Washington, D.C.: HHS, May 1995).

Figure 3: Time Elapsed From Error and Accident Detection to Recall Confirmation, October 1992-April 1993



Note: Numbers may not sum to 100 percent because of rounding.

Source: GAO's analysis of FDA Recall Action Database.

We found no significant differences in FDA's processing time based on the severity of the case. That is, more serious cases were not processed faster than less serious ones. Given the long time FDA takes to go through its formal recall process, blood product safety could be compromised. Clearly, the longer it takes to initiate a recall, the more likely it is that all the product will have already been transfused.

FDA Standards and Guidelines

FDA communicates its requirements through the Code of Federal Regulations and its policies and recommendations through memorandums and letters, compliance manuals and the compliance program, compliance policy guides, and a guide for blood facility inspections. The requirements in the Public Health Service Act; the Food, Drug, and Cosmetic Act; and the C.F.R. are the only mandatory requirements.

We found substantial confusion in the industry on the distinction between FDA regulations and guidance, potentially leading to different interpretations and applications of FDA's requirements and recommendations. As part of our review, we conducted a survey of 45 full-service blood facilities.[11] Many of our survey respondents told us they were unclear about which statements had to be followed and which were only FDA recommendations. Respondents also noted that FDA inspectors sometimes filed reports on significant infractions—forms 483—on the basis of FDA recommendations, that the regulations should be updated to incorporate current memorandums, and that the language in the memorandums should be clarified to indicate which actions are required and which are recommended.[12]

A 1995 Institute of Medicine study on blood safety issues recommended that "when issuing instructions to regulated entities, FDA should specify clearly whether it is demanding specific compliance with legal requirements or is merely providing advice for careful consideration."

The issue has practical implications. The law explicitly requires FDA to prescribe standards for insuring purity, potency, and safety of blood products. However, regarding HTLV testing, FDA has issued memorandums on such procedures; its regulations do not refer to HTLV testing at all. Thus, a facility could be licensed and yet view testing for HTLV as only a recommendation and not a requirement. Nevertheless, not testing for HTLV could directly affect the safety of blood products.

To its credit, FDA has historically issued memorandums to give the industry immediate feedback on its positions on new issues. However, guidelines and memorandums issued for expedience appear to rarely move into the formal regulatory process. While blood facilities often incorporate recommendations into standard operating procedures, the lack of a public comment period—as is required in the formal rulemaking process involved in setting regulations—gives blood facilities no opportunity to address important implementation issues and could lead to inconsistent policies in the industry.

[11]By "full-service," we mean those facilities that conduct the full range of blood collection, processing, and distribution (including viral testing). The response rate to our survey was 100 percent.

[12]An FDA inspector who identifies significant infractions that could affect blood safety files a form 483, noting the objectionable conditions.

FDA Inspections

We found several problems in FDA's inspection process in four broad categories: the use of inspection reports, the timing of inspections, the completeness of inspection reports, and the consistency of inspection reporting. FDA inspects blood facilities every 2 years. Facilities that have received a warning letter or have been found deficient in inspections within the past 2 years may be inspected annually until they pass two consecutive inspections without significant observations. Inspectors file an establishment inspection report with FDA at the close of the inspection, which descriptively narrates the activities covered in the inspection and any problems identified. Observations of potentially unsafe conditions are filed on a form 483 and discussed with management of the facility.

We were told by FDA that it reviews all inspection reports. However, we found that FDA conducts no systematic statistical analyses of inspection reports or forms 483. Without collating, synthesizing, analyzing, and evaluating these data, FDA has no means of assessing overall national compliance, assessing trends by type of facility, identifying the problems of different types of blood facilities, or evaluating the effects of policy changes on implementation rates. By performing these types of statistical analyses, FDA could obtain information on different rates of form 483 observations among district offices, rates of observations by type of activity (for example, donor screening, donor deferral, and viral testing), and rates among types of facilities. We conducted such an analysis, discussed below, which illustrates the feasibility and importance of this task.

We obtained inspection reports and form 483 reports of inspection observations on a nationally representative sample of blood facilities. FDA's own requirement is to inspect blood facilities every 2 years, or more often if significant violations have been detected. However, of the 373 blood facilities in our sample, 45 (12 percent) had not been inspected in more than 2 years. Because our sample represented all blood facilities in the nation, we could project that 348 of the 2,900 registered blood facilities (12 percent) may not have been inspected within the past 2 years.

We also found problems with the completeness of inspection reports. We examined each facility in our sample for whether the inspection report indicated that a particular function (such as viral testing) had been examined. For the purpose of our analysis, if it was mentioned at all in the report, we considered it to have been examined. If it was not mentioned anywhere in any way, we considered that one could not determine whether the area had been examined.

For the time period when checklists were required, we found that 40 of 224 inspections (18 percent) that should have included an inspection checklist did not have one.[13] In many instances, we were unable to determine whether procedures relating to donor screening, deferral, collection, routine testing, viral testing, postdonation information, labeling, quarantining, storage, and "machines" were examined at all in the individual inspections. In fact, for all the areas in our analysis that FDA should have inspected, we could not find indications that it did so in 33 percent (963 of 2,957 areas). Further, we were able to determine in only half of all reviewed reports that inspections covered all activities necessary to ensure compliance.

FDA's current policy is for the inspectors to list on the inspection report only areas that were not covered. That is, when an inspector notes on the report that the inspection was undertaken within a specific compliance program, this means that all blood banking practices covered in the compliance program have been examined. We found that this policy is unreliable in ensuring that activities not covered during the inspection are, in fact, noted on the report. Moreover, without detailed information, FDA supervisors or subsequent inspectors cannot determine what blood banking processes have been examined in an inspection.

For example, at a blood facility inspected in 1994, an inspector found that no lookback procedures had been followed in several cases of reported HIV-positive donors identified since 1990. When we examined the inspection report for this facility for the inspection that took place in 1993, we found no indication that lookback procedures were not being followed. This means either that the 1993 inspection examined lookback procedures and did not find that they had not been carried out since 1992 (according to the 1994 inspection) or that lookback procedures were not observed in the 1993 inspection and this was not noted on the inspection report, which is FDA's stated policy.

As a further measure of the comprehensiveness of inspections, we asked the 45 full-service blood facilities in our survey to what extent FDA examined standard operating procedures in 12 separate areas in their last inspection. In every area except deferral, more than half the respondents indicated that FDA examined standard operating procedures only to a moderate extent or less. Similarly, the respondents reported that FDA does not observe or otherwise examine firsthand major activities in many areas. More than 20 percent reported little or no FDA observation of six different

[13]In September 1994, FDA replaced the checklist with a systems-based guide.

areas. Furthermore, 35 percent of the respondents indicated that FDA evaluated the existence and suitability of only half or fewer of the critical control points their facilities had in place to ensure safety, purity, and potency.

Finally, we have concerns relating to the consistency of inspection reporting. We found significant disparities in inspection reporting across the eight FDA districts we examined. For example, more than 21 percent of form 483 observations related to labeling in one district but only 2 percent in another. We also found statistically significant differences between districts in the issuance of forms 483. In particular, one district issued forms 483 to only 20 percent of inspected facilities, compared with a range of 42 to 52 percent among the districts most likely to issue a form 483. Districts differed in the types of activities that warranted forms 483. Why observations are issued inconsistently is not clear. Either different districts have different problems, or different districts interpret FDA policy differently. Neither we nor FDA can say which is the case. Yet 27 percent of our survey respondents reported that they do not know what to expect from one inspection to the next; what is acceptable to one inspector, they say, may be an unsafe condition to another. And while respondents reported that their most recent inspection team was knowledgeable about blood banking terminology and technology, 45 percent reported a wide variation among inspectors.

Conclusions and Recommendations

While FDA, together with industry, has made great strides in improving the nation's blood supply since the recognition of the risks posed by HIV, we believe that eliminating the vulnerabilities we identified would enhance the safety of blood products.

Therefore we have recommended that the Secretary of Health and Human Services take the following actions:

- Require that blood facilities notify all donors who are permanently deferred (not just those who test positive for HIV) that they have been deferred and the medical reasons for their deferral, so that they do not attempt further donation and can seek further medical care if they desire.
- Require confirmatory testing of all repeatedly reactive viral test results for which there is a licensed confirmatory test, in order for blood facilities to be able to properly counsel donors as to their disease status.
- Require that patients be notified when they have been transfused with blood from a donor whose subsequent donations were found to be positive

by confirmatory testing for any virus for which a confirmatory test is available, not just for HIV. We note that the reasonable time period for tracing back units to recipients varies with each virus, and decisions should be made in consultation with the blood industry.

- Require lookback to identify and remove units from implicated donors that remain in inventory in situations in which those donors' subsequent donations are found to be positive by confirmatory testing for any virus for which a confirmatory test is available, not just for HIV.
- Require unlicensed facilities to report all errors and accidents.

We have recommended that the Secretary take the following additional actions:

- Publish in the form of regulations the guidelines that FDA deems essential to ensure the safety of the blood supply and require that FDA clarify its position on the extent to which facilities must adopt guidelines and memorandums in order to remain in compliance.
- Correct problems that we have identified in FDA inspection processes. FDA should perform statistical analyses of inspection reports, ensure that all blood facilities are inspected in a timely fashion, develop policies for the inspectors to list on inspection reports the activities they observe, and publish better guidance to inspectors on the types of activities that warrant reports on deviations and warning letters.

FDA has been aware of a number of these problems for several years and has initiated some actions to address them. In other cases, the agency has said that our recommendations would be too costly or unnecessary.

We remain convinced, however, that if all the improvements we identified are made, the American public will be better assured that the blood supply is as safe as possible given the current state of technology and medical knowledge. Continued safety depends on the scientific and medical communities' vigilance in detecting and identifying any new threats to the supply.

This concludes my prepared statement, Mr. Chairman. I will be happy to respond to any questions that you or Members of the Subcommittee may have.

Remaining Vulnerabilities in the Layers of Blood Safety

Donor screening	— The style and content of history-taking questionnaires may influence the accuracy and completeness of donors' answers. — Lack of privacy at some facilities may inhibit forthright communication.
Notification	— Lack of universal donor deferral notification could create public health problems. — Lack of universal confirmatory testing of donors testing repeatedly reactive on initial screening assays precludes facilities from having complete information on disease status to use in notifying donors and recipients. — Except for HIV, recipients who have received potentially infectious blood do not have to be notified, and blood facilities do not have to trace and remove units that remain in inventory.
Postdonation information	— Many errors and accidents are discovered as a result of postdonation information that would have excluded the donor had it been known at donation. — Plasma centers report proportionately fewer postdonation errors and accidents than licensed whole blood facilities, despite being subject to the same reporting requirement and collecting equivalent amounts of blood.
Recalls	— Only licensed facilities are required to report. — Plasma centers report proportionately fewer errors and accidents in all areas, despite being subject to the same reporting requirement and collecting equivalent amounts of blood. — Report submissions and subsequent FDA investigations are not always timely.
FDA standards and inspections	— FDA guidance to blood facilities is often ambiguous. — FDA does not perform statistical analyses on inspection reports and forms 483 and therefore cannot assess compliance trends. — Some facilities are not inspected within FDA-established timeframes. — Inspection reports are often incomplete. — Differences exist in form 483 observations among FDA districts, including disparities in what actions constitute need for further action.

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