

Date: August 30, 2010
Reference No.: RPSC10048a

PPTA's Plasma Protein Forum, June 16, 2010
Q&A Session with FDA

Background documents for question 1:

- FDA guidance (04/23/1992) on “Exemptions to permit persons with a history of hepatitis before the age of eleven years to serve as donors of whole blood donors and plasma: Alternative procedures” indicates that “persons with a history of viral hepatitis, prior to 11 years of age, not to be excluded from donating Whole Blood and Source Plasma.”
- FDA guidance (12/22/1993) on “Donor suitability related to laboratory testing for viral hepatitis and history of viral hepatitis” indicates the following in regards to the “History of Viral Hepatitis at the Age of 11 years or later” (page 2, end of first paragraph of section A): “However, persons with a history of a positive (confirmed) test for HBsAg, regardless the age at the time of the positive test, are precluded from donating plasma, or serum under 21 CFR 610.41.”
- FDA guidance (October 2006) on “Implementation of Acceptable Full-length Donor History Questionnaire and Accompany Material for Use in Screening Donors of Blood and Blood Components” – DHQ Question #38 – Have you ever had hepatitis? Flow Chart for DHQ #38 (rev. 2008) indicates: “Donors who have a history of viral hepatitis before the eleventh birthday are acceptable.” This flow chart does not have any information regarding a history of positive test results for hepatitis.

1. Based on the above information, our interpretation is that FDA guidance (2006) – DHQ – Flow Chart #38 (rev. 2008) supersedes FDA guidance (1993). Therefore, we may accept donors who have a history of viral hepatitis before their eleventh birthday, even if they have a history of a confirmed positive test results for hepatitis B or hepatitis C. Is our interpretation correct? (*Ginette Michaud*)

Persons who have had positive test results for HBsAg or anti-HCV or HCV NAT, indicating that they had a hepatitis B or C infection, should be deferred, irrespective of age.

2. Given measles titers are dropping in the general Source Plasma population, is the current measles IVIG titer limit (which is unsustainable over the long term) a relevant marker of consistent IVIG manufacture? Would FDA consider assessment or removal of this limit via their quantitative risk assessment process? (*Ginette Michaud*)

Because the measles antibody titer is important to protecting Primary Immune Deficiency (PID) patients exposed to measles, we are not considering dropping it entirely.

We agree that measles titers in the plasma donor population are likely to fall over time as the higher-titer donor population “ages out.” We also recognize the need for products that protect patients with PID. FDA will address this issue in a public forum at a future date.

3. Can FDA comment on the eSubmitter pilot currently in process? *(Judy Ciaraldi)*

The eSubmitter pilot program for Source Plasma, initiated in September 2009, continues and we are still accepting electronic submissions from the participants. We have extended the pilot period because we hope to receive at least one submission from each category in the pilot program in order to properly test the system.

The eSubmitter system has been designed to accept all types of submissions. This includes applications, supplements, annual reports, and product correspondences. The modules for Source Plasma systems are complete and included in the pilot program. We are working on the modules for blood bank submissions.

The feedback so far from the pilot program participants has been positive. Both the firms and the reviewers have provided very useful comments that have led to some minor revisions and upgrades to the software.

We continue to monitor the CBER_eSubmitter_Program mailbox to provide user support.

FDA was also asked to provide an update on eBPDR and the Direct Recall Classification system. (Mary Malarkey)

The number of BPDRs submitted electronically has increased over the years.

*FY09 - Plasma Centers submitted 77% of their reports electronically
FY10 - Plasma Centers submitted 91% of their reports electronically*

96% of total blood and plasma reports in FY10 (to date) were submitted electronically

The number of recalls that may be processed using the Direct Recall Classification (DRC) system has also increased as changes to the system have allowed more processing of this type. We are in the process of implementing a change that will allow for recalls of more than 18 units to be processed using DRC. Thus far in FY10, 50.65% of plasma recalls have been processed using DRC as compared to 40.22% for FY09. However, we continue to see issues with the timeliness of responses to FDA’s requests for Additional Information (AI) by some in the plasma industry. FDA would appreciate more timely responses.

4. FDA requires that a donation or immunization occur within 7 days of the initial Physical Exam (PE), or the PE must be repeated. Is the requirement satisfied, if the donation is not a complete donation (full volume collected), and, if yes, is there a minimum collection volume, or is it enough that the donor was deemed suitable and a donation was attempted? (*Judy Ciaraldi*)

Yes, the donation requirement is satisfied even if the donation results in an underdraw, unless there is cause for concern. By cause for concern, we mean it depends on the reason for the underdraw.

If the reason for the underdraw is because the donor experienced a reaction, you may decide to examine the donor before the next donation to rule out any underlying illness. Your medical director may decide the exam will consist of a full physical exam as described in your SOP, or a more limited exam as necessary to rule out a condition that could compromise the safety of the donor.

FDA does not have a requirement for a minimum collection volume for a Source Plasma unit.

5. Does FDA have a process for reviewing and updating guidance documents? If so, could FDA please explain? It appears that guidance documents remain in draft for many years or, if finalized, become outdated. For example, the one that governs the antisera IVD manufacturers is a draft guidance from 1992. It requires submission of supplements for variances to this draft guidance, which is burdensome and seemingly unjustified. (*Mark Weinstein*)

FDA's process for reviewing and updating guidance documents is codified in our regulations. Under the Good Guidance Practice (GGP) regulations at 21 CFR 10.115 (f), FDA will periodically review existing guidance documents to determine whether they need to be changed or withdrawn. When significant changes are made to the statute or regulations, FDA will review and, if appropriate, revise guidance documents relating to that changed statute or regulation. Further, any consistent deviation from a guidance document implies that it should be revised.

However, CBER and FDA must prioritize the development and revision of existing guidance documents to ensure issuance of those most critical to public health. We welcome public input in this process and encourage PPTA to comment on the list of possible topics for future guidance development or revisions that are listed in the annual guidance agenda published in the Federal Register. In addition, the public may submit drafts of proposed guidance documents for FDA to consider. For those documents that may appear outdated, remember that guidance documents do not establish legally enforceable responsibilities.

You may choose to use an approach other than the one set forth in guidance, provided the approach complies with relevant statutes and regulations. Manufacturers may discuss an alternative approach with FDA to ensure that it meets regulatory and statutory requirements.

Finally, the 1992 draft guidance mentioned above has been identified internally as needing revision.

6. FDA appears to have a new focus on compliance. At a recent FDLI conference, an FDA attorney stated that “the watchdog is back and has teeth” and compared Commissioner Hamburg to former Commissioner Kessler. What does this mean for our industry? *(Mary Malarkey)*

The initiatives announced by Dr. Hamburg at the referenced FDLI conference apply to all commodities that FDA regulates. We encourage all manufacturers to carefully review these enforcement initiatives, which are available on FDA’s website at <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm176119.htm>

7. Has the FDA given specific instructions to field inspectors to opt to put minor observations on a 483 versus leaving as a discussion item with the center? There seems to be a shift from FDA’s systems approach, *i.e.*, from leaving 483 observations only for systemic problems to leaving 483 observations for one-only occurrences. *(Mary Malarkey)*

There appears to be some confusion about FDA’s systems-based inspectional approach. The Form FDA 483 is a list of inspectional observations that the investigator believes might represent violations of FDA’s laws and regulations. The systems-based inspectional approach focuses inspections into systems that are observed based on the level of inspection.

8. Please provide an update on the revised Warning Letter policies – letters submitted within 15 days of issuance of a form FD-483 will be evaluated in consideration of sending a Warning Letter; formal close-out; web posting. Have there been any changes to the policies post-implementation? Not many close-outs have been posted. Why is that? *(Mary Malarkey)*

The Regulatory Procedures Manual (RPM) has been updated to reflect the new policies. In terms of posting Warning Letter close-out letters, section 4-1-8 of the RPM describes the procedures and timeframes for posting of such letters. Districts or centers should issue close-out letters within a total of 65 working days of having the necessary information upon which to make a decision. Such information might include documents collected during a re-inspection of the establishment that received the Warning Letter.

9. As part of managed review, CBER used to perform a mid-cycle review during the BLA/BLS review. This does not seem to be used consistently. We found the mid-cycle review very helpful and it prevented last minute requests that are difficult to negotiate. Is stopping the mid-cycle review by design? If so, why? *(Mark Weinstein)*

OBRR's mid-cycle review paradigm remains in place. OBRR undertakes a complete review of submitted material that we have in hand at the mid cycle. We then have an interactive review with sponsors in the second part of the cycle to deal with outstanding issues.

However, sometimes information comes to us after the mid-cycle that requires more extensive evaluation, or may come in late in the cycle, which delays communication. Contact Dr. Alan Williams as the ombudsman for dispute resolution if there is a problem related to mid-cycle meetings.

10. Following the immune globulin workshop and BPAC meeting on measles levels, FDA agreed to drop the release test to .48 X CBER standard instead of .6 X CBER standard if certain conditions in a PAS are met. Under what conditions would CBER consider dropping the release specification further?

See response to question 2.

11. FDA recently held a PDUFA reauthorization public meeting. PPTA was able to participate. Will there be more opportunities to provide input? *(Mark Weinstein)*

There will be another public meeting to present the proposed PDUFA package. PPTA should work with PhRMA and Bio to include their needs in the Industry discussions. As required in legislation, there will be regular discussions with patient, consumer and health care stakeholders.

12. Our industry provides therapies for people with rare diseases. We find patient registries to be extremely important resources in these patient populations. We have been disappointed that CBER seems less enthusiastic in accepting patient registry data in lieu of double-blind, placebo-controlled studies, which are extremely difficult to perform in small patient populations. Would you comment on CBER's view on the use of patient registry data in approving new or improved therapies? *(Ginette Michaud)*

CBER agrees that registries are important resources. Available information from registries is often used by the FDA and the regulated industry to design clinical trials to support licensure of products intended for the treatment of rare diseases.

The data to support the approval of a drug must be obtained from adequate and well controlled clinical trials. Note that CBER has considered innovative approaches for

clinical trial design (e.g., the use of historical controls when the natural history of the disease is well characterized; the use of surrogate endpoints).

13. The length of time, from when a reviewer states that a review is completed to the issuance of the license, seems unreasonably long – 11 months in one case and 7 months in another. Why is that? What recourse does a manufacturer have when the timing seems excessively long? This time period doesn't seem to be managed under any timeframe. *(Judy Ciaraldi)*

Just to clarify, the CSO reviewer may have performed the initial review of the submission, but this does not mean that the review of the full submission is complete.

There are many factors involved in the review and approval of a supplement or application. These include:

- *Quality of the original submission and any amendments*
- *The readiness of a firm for the pre-approval inspection*
- *The adequate resolution of any inspectional findings*

Blood and plasma components, including Source Plasma, are not user fee products. However, we voluntarily comply with the PDUFA 2 review timelines. All the blood and plasma submissions are completed within the managed review milestone due date.

If you have identified an irregularity in our review process or you feel you have been treated unfairly compared to other companies, you may bring your concerns to the attention of the OBRR Ombudsman, Dr. Alan Williams.

14. CBER has issued licenses and provided guidance on HIV and HCV NAT tests. What is the status of licensing and recommending use of HBV NAT for source plasma? *(Ginette Michaud)*

At the April 1, 2009 BPAC, the Committee voted in favor of testing blood for transfusion by HBV NAT. FDA normally follows the advice of its Advisory Committee. It is our intention to address this matter in guidance. PPTA, or any other entity, may comment on the contents of draft guidance when guidance is issued for public comment.

15. Can FDA provide the rationale for the current interpretation of the regulation on “day of collection” that donations, where a missing piece of donor-screening information cannot be secured within 24 hours, must be destroyed, *i.e.*, 23 hours is OK, and 26 hours requires destruction? This seems like a waste of perfectly good plasma and a re-interpretation of a regulation that was not originally intended for this rigid interpretation. *(Judy Ciaraldi)*

We published our current thinking on what we understood the requirement to mean in the draft guidance document issued in November 2009, entitled: Recommendations for the Assessment of Blood Donor Suitability, Blood Product Safety, and Preservation of the Blood Supply in Response to Pandemic (H1N1) 2009 Virus.

Our current thinking in the draft guidance document is that because the regulations do not explicitly define the term “day of collection,” a blood establishment may clarify a donor’s response to the donor history questionnaire or obtain omitted responses to questions, within 24 hours of the collection.

Please contact your CSO reviewer if you would like to include this procedure in your SOP.

At this time, we are not at liberty to extend this procedure beyond 24 hours because the regulation states the donor’s suitability must be determined on the day of collection.

16. Could FDA explain the impact the Patient Protection and Affordable Care Act will have on the Agency, in particular CBER? Specifically, we seek information on the progress of the implementing guidance for the abbreviated pathway of biosimilars and CBER’s involvement in the process. *(Mark Weinstein)*

Under the recently enacted Patient Protection and Affordable Care Act (public law 111-148) FDA has been given the authority and responsibility to regulate biosimilar biological products, a newly defined class of medical products. FDA is carefully evaluating the newly enacted biosimilar provisions contained in the health care legislation to determine how best to implement these new provisions in the Act.

FDA has established a cross-center working group that has been charged with the responsibility of establishing policies and procedures to implement the new provisions in a manner that best serves the public health. This working group is being led by Dr. Janet Woodcock, Director of the Center for Drug Evaluation and Research (CDER) and Dr. Karen Midthun, Acting Director of the Center for Biologics Evaluation and Research (CBER).

17. Can FDA provide their current thinking on “Concurrent Plasma” from Blood Centers? *(Mark Weinstein)*

BPAC has endorsed the concept of Concurrent Plasma in 2008 but we have not set product standards nor have we published these standards in guidance or in the regulations. We are considering the comments made at BPAC. Once we have a clear regulatory pathway, we can allow variances for this product.

However, at this time, firms cannot prepare/collect a component called Concurrent Plasma.

18. In light of the recent ACBSA meeting on Male Sex with Males (MSM), can you comment on FDA's current thinking on MSM? (*Ginette Michaud*)

On June 10-11, 2010, the HHS Advisory Committee on Blood Safety and Availability (ACBSA) met to discuss the current Food and Drug Administration (FDA) policy on men who have sex with other men (MSM). FDA's current policy states that men who have had sex with another man at any time since 1977 are deferred as blood donors.

By a vote of 9 to 6, the Committee recommended the retention of the MSM deferral policy at this time. However, the Committee recommended studies to develop a scientific basis for policy alternatives. The government response will depend on an orderly process of review. The HHS agencies will meet with the Assistant Secretary for Health to review the ACBSA recommendations and decide on specific actions.

19. What is current thinking regarding acceptance of donor who fails to provide deferral information at the time of donation but subsequently provides information at a later date. Center investigates and determines donor made an honest mistake. Would FDA expect permanent deferral of donor (i.e., donor provided unreliable answers) or accept center documented investigation and readmittance of donor after the appropriate temporary deferral period? (*Judy Ciaraldi*)

Yes, we would expect the donor to be deferred if it is determined that the donor is an unreliable historian.

A donor may be re-admitted if it is determined the donor made an honest mistake in recall or in understanding the question, provided the donor meets all donor eligibility criteria.

20. FDA guidance regarding NAT testing did not reduce lookback period for NAT positives. FDA thought it best to standardize the LB time period instead of using science. Industry would prefer to make that decision and would like to reduce the LB period when appropriate. Europe uses a 4-month NAT deferral/lookback. Why can't that time be adopted by FDA? (*Ginette Michaud*)

In comments FDA received on the HCV lookback proposed rule, on the NAT for HIV-1 and HCV draft guidance and on the HCV lookback draft guidance, FDA was urged to change the lookback time period from 12 months to a shorter period. However, FDA declined to make the change because of additional scientific information showing that donors infected with HIV or HCV may experience intermittent viremia for a variable period of time prior to a persistently detectable viremia or an antibody

response. Since these episodes of transient viremia may extend over a longer window period than previously estimated, we are requiring a record review period of 12 months before the donor's reactive direct viral detection test.