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FDA Liaison Meeting – 9/30/11

Food and Drug Administration staff met with AABB's FDA Liaison Committee to discuss topics of mutual concern in the areas of donor and patient safety. The committee includes liaisons from AABB, the American Red Cross, America's Blood Centers, Advanced Medical Technology Association, the College of American Pathologists and the Armed Services Blood Program.

CURRENT FDA PRIORITIES AND INITIATIVES

FDA participants reviewed several priorities and initiatives of the agency. Mary Malarkey, director, Office of Compliance and Biologics Quality (OCBQ), noted that enforcement initiatives include an evaluation of the compliance program two years after introduction of a requirement that establishments submit responses within 15 days of receiving Form 483 observations if they want the responses to be considered prior to any additional action by the agency, and a focusing on global strategies to further secure the supply chain. She reported that the Product Quality staff members who review lot releases have been incorporated into the Division of Biological Standards and Quality Control.

Orieji Iloh, MD, medical officer, Division of Blood Applications (DBA), Office of Blood Research and Review (OBRR), Center for Biologics Evaluation and Research (CBER), reminded everyone of the public workshop titled "[Hemoglobin Standards and Maintaining Adequate Iron Stores in Blood Donors](#)," scheduled Nov. 8-9, and Jay Epstein, MD, director, OBRR, focused attention on the public workshop titled "[Data and Data Needs To Advance Risk Assessment for Emerging Infectious Diseases Relevant to Blood and Blood Products](#)," scheduled Nov. 29. Epstein noted that the Office of Biostatistics and Epidemiology is interested in understanding if large health care databases can be used in real time and gave the example of how the databases were mined to study the incidence of Guillain-Barre following administration of flu vaccines.

Genette Michaud, MD, deputy director, OBRR, provided an update on several device guidance documents, noting that CBER is actively engaged in development of these documents. Michaud also noted a recognized need for greater oversight, transparency and predictability of in vitro devices as well as information on FDA's expectation of what content is necessary for a review submission. 1) Regarding laboratory developed tests (distribution and use of which have been occurring under enforcement discretion) FDA intends to follow up the July 2010 public workshop with draft guidance. In response to a question Michaud indicated that guidance for heritable markers testing will be developed separately. 2) [Draft Guidance for Industry and FDA Staff: "Commercially Distributed In Vitro Diagnostic Products Labeled for Research Use Only or Investigational Use Only: Frequently Asked Questions"](#) addresses uncleared products intended for clinical use although they are labeled "Research Use Only" or "Investigational Use Only." (See additional notes under discussion topic "Laboratory Developed Tests"). 3) [Draft Guidance for Industry and Food and Drug Administration Staff: "In Vitro Companion Diagnostic Devices"](#) discusses therapeutic products that depend on the use of an in vitro companion diagnostic device (or test). The guidance explains the need for FDA oversight of companion diagnostic devices. It also clarifies that, in most circumstances, if use of a companion diagnostic device is essential for the safe and effective use of a therapeutic product, both the diagnostic device and the therapeutic product should be approved or cleared contemporaneously by FDA for the use indicated in the therapeutic product labeling.

Lore Fields, MT(ASCP)SBB, consumer safety officer, Blood and Plasma Branch, Division of Blood Applications (DBA), informed participants that the eSubmitter program developed by CBER for whole blood and blood components had completed pilot testing and has been available for use since Aug. 5. FDA staff plan to offer an education session at the AABB Annual Meeting in San Diego. Fields noted that facilities choosing to continue with paper submissions can still download the materials.

AABB INITIATIVES AND CURRENT PRIORITIES

James P. AuBuchon, MD, president, AABB, provided information on the association's focus on patient-centered blood management, an evidence-based, multidisciplinary approach to optimizing the care of patients who might need transfusion. AABB is committing resources and efforts to reach out to clinicians in hospitals to improve patient outcomes:

- Eight webinars and two audioconferences in 2012 in partnership with Society for the Advancement of Blood Management
- Patient-centered blood management primer
- Guidelines for patient-centered blood management
- A redesigned website

SPECIFIC TOPICS DISCUSSED WITH FDA

Follow-up to Public Workshop on Laboratory Developed Tests

Blood establishments continue to consider what the implications might be from increased FDA activity with laboratory developed tests following the 2010 workshop. The highest level of concern is in the area of reference tests and molecular testing. FDA participants were asked to provide an update of the agency's current considerations for these areas of testing in which blood establishments have long been engaged.

In June the agency published a draft guidance titled "[Commercially Distributed In Vitro Diagnostic Products Labeled for Research Use Only or Investigational Use Only: Frequently Asked Questions](#)." Laboratories performing such testing routinely identify the results as supplementary to phenotyping with licensed reagents, when the latter are available, but the genotype may still be clinically useful in deciding which donor units may be most appropriate for a patient to receive. To date the FDA has not taken steps to prohibit the distribution of these genotyping reagents. The agency was asked to comment on how this thinking, if released in its current form as a guidance document, would be applied to the reagents used in red cell genotyping, especially their availability.

Sheryl Kochman, deputy director, DBA, and Jay Epstein responded, saying that the division (Blood Applications) is in close touch with the Center for Devices and Radiological Health (CDRH), primary "owner" of the applicable guidance documents, with the intent of ensuring there is no adverse fallout for patients. OBRR supports the risk-based approach that CDRH intends to use as FDA gradually pulls back from the enforcement discretion that has been applied to most laboratory developed tests. In the risk-based approach that FDA takes, molecular tests will likely be one of the first categories of tests required to be submitted for clearance. In the meantime what is paramount is a close look at the claims that the manufacturers are making; tests that are known to be, or likely to be, used for clinical purposes might be more appropriately marketed as IDEs, or investigational device exemptions, rather than as RUO/IUO, or research use only/investigational use only.

Computer Crossmatch

FDA issued a guidance document with final recommendations in April 2011 titled " ['Computer Crossmatch' \(Computerized Analysis of the Compatibility](#)

Between the Donor's Cell Type and the Recipient's Serum or Plasma Type)." The topics for discussion were concerned with the recommendations found in **Section IV, "Elements of a Computer Crossmatch System."**

The first discussion related to the recommendation for a unit of blood collected from a donor with RBC antibodies:

D. Donor RBC Antibody Assessment. If tests for unexpected antibodies are positive, blood and blood components intended for transfusion must be labeled by the blood collecting facility with the name of the antibody (21 CFR 606.121(e)(1)(iii), (e)(2)(ii) and (e)(4)). Using this information, you should determine if the donor has clinically significant RBC antibodies. If the donor has clinically significant RBC antibodies, you should not rely on a computer crossmatch. Under those circumstances, your procedures should provide for compatibility testing using serologic crossmatch techniques capable of detecting such clinically significant antibodies.

At least one facility contacted FDA when the guidance document was published and noted, since there is no scientific basis for this recommendation, that it had been performing electronic crossmatches on such units. The facility was told it could continue its current practice.

In discussion with FDA participants, Liaison Committee members noted as an example of a clinically significant donor antibody that undergoes electronic crossmatches the frequent situation when Type O units are crossmatched for Type A patients. FDA staff suggested that it would be helpful if data showing the safety of crossmatches involving clinically significant donor antibodies were submitted to FDA.

The second topic concerned the recommendation related to recipient ABO/Rh typing:

B. Recipient Data Elements. 2. Recipient ABO/Rh (D) Type and Interpretation. You should determine a recipient's ABO and Rh (D) antigens (Ref. 11). You should either perform or maintain a record of a second test, confirming the recipient's ABO/Rh (D). For example, this second test may be a record of a test performed previously, or a repeat test on a second, separately drawn specimen. Repeating ABO and Rh (D) tests on the same specimen is not recommended, as the major cause of ABO errors is "wrong blood in tube" (WBIT). Performing tests on two separately drawn specimens is *preferred*, as this lessens the likelihood of errors because specimens have been drawn in error. In certain situations, however, only one specimen may be available for testing, such as in emergencies or when only one sample is received for home transfusion. At those times, repeat testing may be performed on the same specimen, but the repeat test should be performed either by a different technologist or by the same technologist using different reagents. (*Emphasis added.*)

This language seems to – almost – recommend ABO typing on a second (distinct) sample before using the computer crossmatch protocol. FDA participants were asked to explain the strength of the agency's perception of this as a preferred approach.

FDA participants were of the opinion that routine practice should be two independent samples and stated an understanding that exceptions occur. They also noted an understanding of the concerns with the language as pointed out and suggested that after further considerations it might be that technical amendments to the guidance document could be used to clarify both situations that had been brought to their attention. Although the docket for comments to the guidance is officially closed, FDA participants noted that proposed wording to clarify these issues could still be submitted, and they indicated that suggested wording would be welcome.

Bacterial Screening of Platelet Components

When discussing this topic at the March 2011 AABB FDA Liaison meeting, FDA noted that the requirements related to a release test for bacterial contamination in platelet products were discussed at the March 2006 Blood Products Advisory Committee (BPAC) meeting. Regarding application of effective testing methods to detect bacterial contamination in platelet products, FDA participants at the March 2011 Liaison meeting further noted that the agency encourages the use of both technologies currently available (culture and point of issue), as they both contribute to the safety of the transfused product. FDA participants also indicated that FDA might consider a guidance that discussed the various methods available.

Experience from application of the Verax PGD[®] bacterial detection test has now been accepted for publication in *TRANSFUSION*. This manuscript illustrates again that the currently used approach of automated culture of platelet units early in storage misses a substantial proportion of bacterially contaminated units.

The agency was asked for an update on its considerations of formal, public recognition of this risk of transfusion, and/or development of guidance to blood collection establishments that would reduce this risk through pre- and/or post-storage detection method(s).

FDA participants remarked that while they are aware of the results of the recent Verax PGD[®] study published in TRANSFUSION, as noted above, they also noted that the false positive rate is considerable. FDA continues to encourage sponsors to bring products forward for review.

Pathogen Inactivation

FDA spokespersons at a recent Liaison meeting referred to "first generation" pathogen inactivation indicating that all current techniques are first generation, thus implying that a second generation must be coming. There was also an inference that none of the first generation approaches was acceptable. The agency was asked to respond to the concern that the path forward would appear to be very difficult if this interpretation is correct.

According to FDA participants, the agency has no inherent bias against first generation testing, but noted that unexpected toxicities have been an issue with some studies and therefore additional studies must be performed to address this concern. They also noted that red cell studies had problems with antibodies and the recent platelet study has unresolved issues. FDA has looked at some European experiences and databases but found it hard to extract meaning from existing passive-reporting hemovigilance databases. FDA participants stressed that they remain open to reviewing pathogen inactivation systems and working with sponsors to design additional studies that will hopefully resolve open issues.

Licensure of Plasma for Further Manufacturing

FDA considerations for licensure of this component were reviewed at the April meeting of the Blood Products Advisory Committee. The committee offered advice based on the questions presented to them. In addition, FDA acknowledged the importance of developing the pathway so that future products would be eligible for inclusion. The agency was asked to comment on the current status of this initiative and to advise whether the Liaison Committee or the Plasma Task Force can be of assistance.

FDA participants responded that this continues to be a major initiative. They are continuing to review the plasma standards that were approved at the April BPAC meeting and the regulations that will require revision. Once a regulatory pathway is developed, including identification of the required revisions to regulation, the agency plans to issue a draft guidance document. After that, the agency would expect to be able to review variance requests (based on the draft guidance) while rulemaking progresses. In response to the offer of assistance, FDA participants noted that they have no further questions for the task force.

Donor Written Statement of Understanding

At its meeting in April, the Blood Products Advisory Committee provided advice to FDA on elements proposed by the agency that blood collectors should cover when interacting with donors. The BPAC advised FDA that although many of the proposed elements are necessary to the process of informing donors, flexibility is vital to allow establishments to interact with donors. Regulating the methodology, or in many instances the language, to be used would not result in

an informed donor. AABB presented information to the committee showing how the Standards for Blood Banks and Transfusion Services parallel the elements presented by FDA. America's Blood Centers explained the formation of its working group that plans to create model education and consent materials focused on the elements not related to transmission of infectious disease. During the open public hearing at the BPAC meeting, AABB and ABC requested that FDA allow donor education to proceed as a development from industry rather than being disseminated through guidance or regulation.

The Liaison Committee requested the opportunity to discuss with FDA participants the importance of the donor education process being developed by industry.

FDA received an update on the progress of ABC's working group to produce model education, informed consent and parent/guardian permission materials comprehensible to donors recruited to give blood in community blood centers. The working group's current focus is on materials intended to educate donors about the donation process. The working group intends to obtain stakeholder input, ensure language is appropriate to its audience and perform pilot studies before presenting the finished materials to stakeholders and FDA. FDA participants indicated that the information presented was very helpful and suggested that it be submitted to the docket created for the November 2007 proposed rule "Requirements for Human Blood and Blood Components Intended for Transfusion or for Further Manufacturing Use" even though the docket has closed.

TSEAC Discussion of vCJD Risk Associated With Time Spent in Saudi Arabia

The [Transmissible Spongiform Encephalopathies Advisory Committee](#) at its August meeting advised the FDA to add Saudi Arabia to the countries against which donor travel and residency should be assessed. Several members of the committee questioned whether deferrals based on modeling could be eliminated, because sufficient time has passed to produce actual data.

The agency was asked how and when it will transition to the use of actual data rather than relying on modeling to assess risk for variant Creutzfeldt-Jakob disease, or vCJD.

FDA staff reviewed the history of blood safety policy relevant to vCJD that was developed beginning in 1996. It was based on recognition that BSE (bovine spongiform encephalopathy) in the diet was the source of vCJD, and vCJD in the blood had the potential to be transmitted. The accumulation of 15 years of data should decrease reliance on modeling data; however, when risks in France were being assessed, modeling was more accurate than the data that had accumulated. Currently FDA is of the opinion that modeling continues to have value and that the best path forward includes use of both tools. Through the Veterans Administration health system the U.S. military will be able to continue to accumulate good data; to date, no cases of vCJD have occurred in active duty members or family members deferred for potential exposure to the BSE agent.

BPAC Discussion of Interdonation Intervals in Severe Emergencies

[Two proposals for shortened interdonation intervals](#) were presented to the BPAC for discussion. FDA proposed that donors who met the criteria of an FDA-approved, and conservative, apheresis red cell nomogram when they donated a whole blood unit at the previous donation could be eligible in a severe emergency to donate a second unit at 4 weeks, or at 48 hours, if certain other criteria were met. The proposal for a second unit at 48 hours included a physician review. The committee advised the FDA that donors should be allowed to donate under both proposals and that a physician review was not necessary at 48 hours.

The Liaison Committee appreciates the agency addressing emergency donor measures with the BPAC and providing them with the necessary background they needed to understand the issues. The Liaison Committee is interested in discussing other donor criteria, such as assessment of donor travel, that might be included for consideration in an emergency measures guidance.

FDA participants noted that the measures discussed at the BPAC were an outgrowth of discussions that began during the influenza pandemic. Any emergency measure must be fully addressed with respect to benefits, risks and practicalities in an emergency. It was suggested that any additional criteria should be submitted to the docket created for the November 2007 proposed rule "Requirements for Human Blood and Blood Components Intended for Transfusion or for Further Manufacturing Use," specifically addressing revisions to 21 CFR 640.120(b). Suggestions included hemoglobin levels, malaria travel, interdonation levels (beyond the recent discussions as long as the donor met all other criteria), and hemoglobin criteria for platelet donors.

Quarantine Release Errors (QRE) Workshop

The description on the CBER website of the Sept. 13 [public workshop](#) includes the following statement:

There has been a recent focus on QREs related to the release of units with incomplete or absent testing for transfusion-transmitted infectious diseases. On June 10-11, 2010, the HHS Advisory Committee on Blood Safety and Availability (the Committee) met to discuss the current FDA blood donor deferral policy on men who have sex with other men. While the committee recommended that the current deferral policy not be changed at the present time, it found the current policy to be suboptimal in permitting some potentially high-risk donations while preventing some low-risk donations. The committee made a number of recommendations and indicated that HHS should take action to investigate and reduce the risk of QREs in blood collection establishments.

The Liaison Committee asked the agency to discuss the outcomes of this workshop and especially to explain how it believes the outcomes can affect the current MSM deferral policy.

FDA participants noted that the agency's concern is that high-risk units (MSM) might enter the inventory. At the workshop, marker positive units and other issues were discussed. Human errors and process controls were determined to be the cause of most quarantine release errors; errors relating to BECS (blood establishment computer systems) had minimal effect. Conclusions of the workshop were that 1) common definitions of quarantine release errors are needed; 2) a method to capture critical data is needed; and 3) a method to stratify QREs by risk should be developed. FDA suggested a task force is needed to discuss outcomes of the workshop. AABB agreed to set up the task force.

Warnings Against Blood Donation in FDA-Approved Package Inserts

The AABB Donor History Task Force maintains a [Medication Deferral List](#) that is intended for use in screening blood donors. Medications appear on the list if the drug adversely affects the potency of the blood product or if a single exposure to the level of residual drug that may be present in a blood component poses risk to recipients (especially in pregnancy). The task force is aware that although the Center for Drug Evaluation and Research reviews and approves medications and associated labeling and package inserts, no mechanism is in place to alert the Center for Biologics Evaluation and Research when a newly approved medication contains a warning against blood donation. The task force appreciates the efforts that have been made by colleagues in the Office of Blood Research and Review to establish a mechanism and the few ad hoc contacts that have occurred. However, a formal mechanism has not been established between the two centers so that CBER knows when CDER has approved a drug with labeling that warns against blood donation.

This does not seem to be satisfactory when according to [FDA Memorandum: "Deferral of Blood and Plasma Donors Based on Medications \(7/28/93\)":](#)

Blood products manufactured from donors receiving certain medications may contain significant levels of these medications. Transfusion of these products could result in adverse effects to certain recipients or to the developing fetus of a pregnant recipient...

...It is the responsibility of the medical director of the blood establishment to determine policies for deferral of donors taking medications other

than the ones mentioned above.

The Liaison Committee asked to discuss how a system of communication could be established.

The update from FDA was that the two Centers (CBER and CDER) have established a dialogue and are focusing on a process whereby the CDER review process will incorporate a discussion of whether blood donation should be an issue. Committee members encouraged OBRR to be involved with CDER in this review, because the decision whether blood donation should be avoided is complex.

Guidance Documents and Rules

The following documents and rules continue to be of interest to the AABB FDA Liaison Committee and to the membership.

- "Implementation of an Acceptable Abbreviated Donor History Questionnaire and Accompanying Materials for Use in Screening Frequent Donors of Blood and Blood Components."

A guidance topic with this title appears on the Annual Guidance Agenda for 2011. AABB first submitted its abbreviated questionnaire to FDA in March 2002. In December 2003 and again in March 2005, the BPAC indicated support for this abbreviated screening tool. During the past almost 10 years, the AABB Donor History Task Force has worked with the assigned FDA liaisons to address questions or concerns posed by reviewers at the agency. A subgroup of the task force spent an extensive amount of time developing a post-implementation study that will be voluntarily utilized. In August the task force submitted another update to provide a clarification of the definition of a "frequent donor."

AABB notes that the FDA has approved for use two other abbreviated questionnaires for whole blood donors and that the draft guidance document recognizing the abbreviated and full-length DHQs for source plasma donors was published earlier this year.

- "Use of Nucleic Acid Tests on Pooled and Individual Samples From Donors of Whole Blood and Blood Components (Including Recovered Plasma, Source Plasma and Source Leukocytes) To Adequately and Appropriately Reduce the Risk of Transmission of Hepatitis B Virus."

This guidance topic was listed on the Annual Guidance Agenda for 2011. The BPAC discussed it in April 2011 as it relates to source plasma donors and in 2009 in relation to whole blood donations.

- "Revisions to Labeling and Storage Requirements for Blood and Blood Components, Including Source Plasma."

Interest remains in seeing this published as a final rule so that, among other things, thawed FFP (fresh frozen plasma) and PF24 (plasma frozen within 24 hours of collection) will no longer require a variance to be kept 24 hours after thaw. These items first published as proposals in 2003.

- A guidance document allowing blood collection from U.S. residents who have visited Quintana Roo, Mexico, without deferral for malarial risk.

This guidance document remains unpublished despite the support of the agency staff that proposed the change in deferral policy to the BPAC, the BPAC committee and the blood community.

Updates were not available.

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