

BLOOD PRODUCTS ADVISORY COMMITTEE  
101st Meeting, August 3, 2011  
The Hilton Washington DC North/Gaithersburg  
620 Perry Parkway  
Gaithersburg, MD 20877

**Issue Summary**

**Title: Maintaining a Safe and Adequate Supply of Donated Blood During a Severe Emergency**

**Issue: FDA seeks the advice of the BPAC on current considerations to increase flexibility for the collection of Whole Blood for transfusion during a severe local, regional or national emergency by permitting reduced interdonation intervals for eligible Whole Blood donors under specified conditions.**

**I. Introduction:**

This BPAC discussion will provide an overview of government and private sector preparedness and planning for maintaining an adequate blood supply during emergency conditions. In addition to providing an overview of emergency measures already established, FDA will introduce as current considerations two modifications to current Whole Blood interdonation intervals for eligible donors under specified conditions during a severe emergency. These considerations parallel current practices for apheresis collection of red blood cell (RBCs) with the goal to improve the flexibility of blood establishments to safely collect Group O and other types of Whole Blood from eligible donors under severe emergency conditions

**II. Background:**

**A. Current National Response Structure for Blood and Blood Product Supply**

Under Emergency Support Function (ESF #8) of the Department of Homeland Security's National Response Framework (Public Health and Medical Services Annex) the Department of Health & Human Services (DHHS) and its governmental and non-governmental partners are responsible for efforts to help ensure blood and blood product safety and availability during an emergency.<sup>1</sup> ESF #8 defines the roles and responsibilities of HHS and defines a liaison relationship between HHS and the AABB Interorganizational Task Force on Domestic Disasters and Acts of Terrorism (Disaster Task Force) to assist in blood supply logistics and the coordination of national public blood messages on the need to donate.

Functionally, the Disaster Task Force ensures coordination of blood supply logistics during an emergency or disaster, and fosters collaboration and partnership between government agencies, nonprofit organizations and the private sector. The Disaster Task

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<sup>1</sup> Information about Emergency Support Functions is available at: <http://www.fema.gov/emergency/nrf/>

Force includes representatives from major blood collection organizations, as well as government entities such as HHS, FDA, the Centers for Disease Control and Prevention (CDC), and the Armed Services Blood Program Office. Also included are private and nonprofit stakeholders such as the Advanced Medical Technology Association (AdvaMed), America's Blood Centers, the American Red Cross, American Hospital Association, College of American Pathologists and the Plasma Protein Therapeutics Association (<http://www.aabb.org/programs/disasterresponse/>). The Task Force meets on an ongoing basis for planning and preparedness purposes. Immediately following emergencies and disasters which may impact the blood supply, the Task Force meets to assess the circumstances and to coordinate members' response activities. When a particular region or locality is impacted, representatives from blood establishments in any affected area are invited to participate in the Task Force's activities. The Task Force makes recommendations to blood establishments for meeting community needs during emergencies and helps to coordinate delivery of blood and blood components and necessary supplies to affected communities.

## **B. The US Blood Supply: To what extent is it vulnerable?**

The United States has a large network of blood centers and a generally robust blood supply. To date, the United States has not experienced critical shortages of blood or blood products as a result of an emergency or disaster and it is widely believed that blood already on hospital shelves would be adequate to meet all but the direst emergency needs. However, it is important to recognize that the adequacy of the US blood system has not to-date been tested by a severe emergency, such as a large earthquake in a major city, a multi-site nuclear or terrorist event, or a severe pandemic, where a significant number of blood donors, blood establishment staff, and vendors of blood-related supplies may be affected.

It is possible that a future emergency or disaster of sufficient severity, scope, or duration could at least temporarily disrupt the US blood supply as well as the ability of the Disaster Task Force to expeditiously assess and alleviate shortages. It is generally accepted that approximately 50% of blood used in the US is necessary for non-elective patient support, therefore patient morbidity and mortality could occur rapidly in a local or regional emergency where needed blood was not available. In the context of planning for the recent H1N1 Influenza pandemic, the AABB Pandemic Task Force sought potential regulatory accommodations from FDA that would facilitate maintenance of necessary blood supplies, including consideration of modified interdonation intervals for Whole Blood donation. While it has not been proven, reduced interdonation intervals (limited to donors selected to assure safe blood collection) would, in theory, permit an immediate increase in blood collections from an otherwise constrained donor base.

## **C. Experience with Blood Shortages in a Disaster**

While the nature, severity, geographic impact and duration of any future local or national emergency are unknown, past experience may provide insights and help identify potential issues to consider in emergency preparedness efforts. Two emergencies over the past decade, namely the events of September 11<sup>th</sup>, 2001 and the H1N1 influenza pandemic,

prompted responses from FDA because of actual or potential impact on the blood supply. On September 11, 2001 FDA posted recommendations on the CBER webpage to assist in the collection and processing of donated blood that exceeded 300% of normal collection volumes in some areas based on an initial estimate that there might be tens of thousands of potential recipients in urgent need of transfusions in New York City. In 2009, FDA published draft guidance pertaining to pandemic influenza (H1N1) and the blood supply, which was revised to contain general recommendations and finalized in November 2010 as “Guidance for Industry: Recommendations for Blood Establishments: Training of Back-Up Personnel, Assessment of Blood Donor Suitability and Reporting Certain Changes to an Approved Application.” (Ref. 1).

A recent FEMA National Level Exercise was based on the scenario of a major earthquake in the New Madrid Seismic Zone potentially impacting states including Arkansas, Kentucky, Mississippi, and Missouri. Although not designed to challenge the blood supply, a hospital participating in the exercise did seek regulatory accommodations from FDA to expand local blood supplies. The experience of other nations, such as Japan, Haiti and New Zealand, suggests that a severe earthquake could lead to difficulties in maintaining the supply of blood and blood products.  
([http://www.fema.gov/media/fact\\_sheets/nle2011\\_fs.shtm](http://www.fema.gov/media/fact_sheets/nle2011_fs.shtm)).

**As a result of previous experience with medical emergencies, disaster situations in the US and abroad, and insights from preparedness exercises, FDA has in place a number of regulations and guidance documents that provide blood collection establishments with considerable discretion and flexibility to make exceptions to current standards in order to make blood available during emergencies. These are summarized in Appendix A.**

### **III. Proposals for Reduced Interdonation Intervals In Severe Emergencies**

Considering the parallels with current practices for two unit RBC apheresis and platelet apheresis as discussed below, FDA seeks the BPAC’s advice regarding the safety of a one time annual reduced interdonation interval of 4 weeks (without physician review) and 48 hours (with physician review) for Whole Blood donation in emergencies for repeat donors who meet a specific double RBC apheresis nomogram and all other donation requirements. Presentations during the BPAC session will discuss blood donation physiology, blood center experience with two unit RBC collections (Ref. 2), and practical aspects of emergency response at the blood establishment level.

#### **Proposal #1.**

- **For use under emergency conditions only.**
- **Manual collection of a second Whole Blood (WB) unit no less than 4 weeks since the last WB collection, (i.e. instead of eight weeks) from donors who qualify based upon a specific two unit RBC apheresis collection nomogram at the time of the second donation.**
- **Physician review not required prior to 2<sup>nd</sup> donation.**
- **Donation with a reduced interdonation interval limited to one time per year**

- **Applicable only to donors who have not provided other collections (e.g. plateletpheresis, plasmapheresis) in the 8 week interval prior to the collection of the first Whole Blood unit.**
- **Subsequent deferral from all blood donations for sixteen weeks after the second WB donation.**

In accordance with 21 CFR 640.3(b), Whole Blood donors are not allowed to donate more than one time in an eight week period; except that under 21 CFR 640.3 (f), a donor may donate Whole Blood more than once in eight weeks if at the time of donation the person is examined and certified by a physician to be in good health.

During a severe local or national emergency impacting the blood supply, FDA is considering a one time annual reduced inter-donation interval of a minimum of four weeks for donors of Whole Blood. This procedure would be limited to repeat donors (male or female) who meet a pre-defined height/weight/hematocrit nomogram which is currently in use for double RBC collection by apheresis, as well as current donor eligibility requirements. Under emergency conditions, FDA is considering whether to allow the donation to take place at  $\geq 4$  weeks interval without the physician examination and certification that are required by current regulations. For sixteen weeks after the second donation, the donor would be deferred from all forms of donation. Total Whole Blood or RBC donations for an individual should not exceed the blood establishment's annual limit as specified in SOP.

- **Proposal #2:**
- **For use under emergency conditions only.**
- **Manual collection of a second Whole Blood (WB) unit no less than 48 hours since the last WB donation from donors who qualify based upon a specific two unit RBC apheresis collection nomogram at the time of the second donation.**
- **Physician review required prior to second donation**
- **Donation with a reduced interdonation interval limited to one time per year.**
- **Applicable only to donors who have not provided other collections (e.g. plateletpheresis, plasmapheresis) in the 8 week interval prior to the collection of the first Whole Blood unit.**
- **Subsequent deferral from all donations for sixteen weeks after the second WB donation**

Similarly, FDA seeks the advice of the BPAC regarding the safety of collecting a second manual Whole Blood collection from an eligible donor after a very short interval (48 hours). This procedure would be limited to repeat donors **who qualify based upon a specific two unit RBC apheresis collection nomogram**. The 48 hour interval between Whole Blood collections is intended to allow time for replenishment of the intravascular fluid volume. Physician review of the second donation would be required. Deferral from future donation and all other parameters would be the same as for the four week interval described above.

#### **IV. Discussion of the Proposals**

Nomograms for double RBC collection by apheresis (based upon FDA-cleared manufacturer's instructions for use) have been in place for several years and have an established record of safety and donor acceptance. One commonly used FDA-cleared nomogram indicated below can be easily adapted to a Whole Blood collection setting under emergency conditions. The concept of the nomogram, in association with a sixteen week period of deferral, is to assure that donors are not placed at risk for undue loss of iron. Additionally, use of the nomogram prevents removal of a fluid volume in excess of that which would not be tolerated by the donor.

##### **A. Limitation of Red Cell (and Iron) Loss**

The volume of RBCs removed during a single Whole Blood collection (~180-200 ml for a 500 ml collection) is the same (or less under some apheresis device nomograms) as the volume of RBCs removed by a single RBC collection by apheresis. The volume of RBC removed by two Whole Blood unit collections (~360 ml) would likewise be the same or less than the volume removed by a double apheresis RBC collection. Donors are deferred from any blood donation for 16 weeks following a double RBC apheresis procedure to provide time for replacement of iron and recovery of the donor's normal hematocrit.

The most conservative FDA-cleared donor eligibility nomogram currently in use for two unit RBC apheresis for larger donors allows for safe removal of up to 420 ml of RBC per collection. As the red cell loss from two 500 mL Whole Blood collections may approximate 420 mL, the use of this specific algorithm helps to provide assurance that a smaller person would not be placed at risk for excessive RBC or fluid loss.

	<b>Weight</b>	<b>Height</b>	<b>Hematocrit</b>	<b>Hemoglobin</b>
<b>Males</b>	<b>150</b>	<b>5'1"</b>	<b>42</b>	<b>14.0</b>
<b>Females</b>	<b>175</b>	<b>5'5'</b>	<b>42</b>	<b>14.0</b>

The nomogram-based eligibility criteria are more stringent for female donors due to the increased prevalence of low iron stores among female repeat donors.

##### **B. Limitation of Volume Loss**

Fluid loss as a result of donation is also an important consideration. The devices commonly used for double RBC apheresis infuse 250-500 ml of saline following RBC collection. A 500 ml Whole Blood collection results in 500ml volume loss, and total volume is replenished quickly by the body. The minimum four week and 48 hour

interdonation intervals under consideration for Whole Blood unit collection are viewed as sufficient for complete replacement of the intravascular fluid volume.

Additionally, the experience with safety of plasmapheresis under current donation standards (2x/week with an interval of not less than 48 hours) also supports the safety of fluid volume replenishment within a 48 hour period.

### **C. Advantages of Reduced Interdonation Intervals for Whole Blood Collection in Severe Emergencies**

Blood component collection by apheresis has expanded greatly over the past decade and as of 2008 represents 11.3% of RBC units collected annually in the US, most of which are double RBC collections (Ref. 3). Advantages include the ability to customize the components collected based upon donor blood group and hospital demand, as well as the efficiencies gained in donor recruitment, staff time, and testing. In an emergency situation, it is expected that apheresis procedures would be continued and expanded. However dependence on automated collections may become less feasible if an emergency situation becomes severe.

#### *Limited availability of trained staff:*

Staff who conduct apheresis procedures are highly trained for use of specific equipment types. To the extent that staff members are not available due to external commitments or diversion to other critical blood establishment functions, back-up staff with adequate training for automated collections may not be available. In contrast, while Whole Blood collection also requires thorough training, the procedures are comparatively simple and a larger proportion of staff or available medical/technical personnel would be capable of collecting Whole Blood units.

#### *Fixed and Portable Devices:*

Apheresis device performance is validated for use in a controlled setting. Apheresis devices in use at fixed collection sites permit the selective and simultaneous collection of RBC, platelet, and plasma products. The devices cannot be easily re-located within a damaged facility. In addition, a concurrent need for platelets during an emergency may occupy most of the fixed site apheresis capabilities. Portable apheresis devices for use on mobile collections can collect double RBC volumes, however the available number of portable units remains somewhat limited.

#### *Electrical outages:*

While portable apheresis devices can operate on battery power in the event of an outage, this is primarily to allow completion of an ongoing collection and short term operation. Long term dependence on battery power for RBC collection during a disaster is unlikely to be feasible. In contrast, Whole Blood collection is simple and relatively independent of environmental conditions (assuming that appropriate blood unit storage is available.)

#### *Available collection supplies:*

It is important to recognize that many blood establishments maintain “just-in-time” supply inventories. The maintenance of Whole Blood and/or apheresis operations in the course of a prolonged emergency is likely to be dependent upon the replacement of supplies. Maintaining adequate on-site stocks of blood bags (as opposed to apheresis collection sets) for emergency use may be more feasible for sites that choose not to be totally dependent on external suppliers.

## V. Questions for the Committee:

Question 1. Do the available data support the safety of collecting two Whole Blood units during a severe emergency with an interdonation interval of  $\geq 4$  weeks from donors who are eligible under the proposed nomogram and under the conditions outlined below including:

- Limited to repeat donors
- Physician review not required for second donation
- Sixteen week deferral from all donations following second collection
- No apheresis donation between the two Whole Blood collections
- Complies with RBC donation limits established in blood establishment SOP

Question 2. Do the available data support the safety of collecting two Whole Blood units during a severe emergency with an interdonation interval of  $\geq 48$  hours from donors who are eligible under the proposed nomogram and under the conditions outlined below including:

- Limited to repeat donors
- Physician review required for second donation
- Sixteen week deferral from all donations following second collection.
- No apheresis donation between the two Whole Blood collections
- Complies with RBC donation limits established in blood establishment SOP?

## ***REFERENCES***

1. “Recommendations for Blood Establishments: Training of Back-Up Personnel, Assessment of Blood Donor Suitability and Reporting Certain Changes to an Approved Application,” Final Guidance for Industry and FDA Staff. Dated November 2010. <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm235785.htm>

2. Benjamin, RJ, et al. The relative safety of automated two-unit red blood cell procedures and manual whole-blood collection in young donors. *Transfusion* 2009; 49:1874-1883.

3. Report of the U.S. Department of Health and Human Services. The 2009 national blood collection and utilization survey report. Washington, D.C: U.S. Department of Health and Human Services, Office of the Assistant Secretary for Health, 2011.

## Appendix A

### **Existing FDA Emergency Measures, Regulations and Guidance (Note that “you” refers to blood establishment manufacturers)**

In times of emergency, FDA reminds the blood community of existing regulatory pathways, and provides specific recommendations that may be helpful should an emergency reach a level of severity that significantly impacts the availability of blood and blood components. Current regulations provide blood collection establishments with discretion and flexibility with respect to certain requirements such as donor eligibility criteria, shipping of products between states, and emergency use.

#### **1. Release or shipment prior to testing**

Under current regulations, blood or blood components may be released or shipped prior to completion of testing for evidence of infection due to communicable disease in appropriately documented medical emergency situations. Such units must be labeled according to 21 CFR 606.121(h); the testing is completed as soon as possible after release or shipment; and the results are promptly provided to the consignee (21 CFR 610.40(g)). The release or shipment of units prior to testing occurs rarely. In such an event:

- You must appropriately document the medical emergency;
- You must label the blood or blood components shipped in an emergency prior to completion of required tests with the following:
  1. The statement "FOR EMERGENCY USE ONLY BY \_\_\_\_\_" ;
  2. The results of any tests prescribed under 21 CFR 610.40 and 640.5 (a), (b), or (c), completed before shipment;
  3. An indication of any tests prescribed under 21 CFR 610.40 and 640.5 that were not completed before shipment.
- You must promptly complete the required tests as soon as possible after release or shipment and promptly provide the results to the consignee.

#### **2. Product Identification and Recordkeeping**

Under 21 CFR 606.100, you must have SOPs which include, among other things, the processing and distribution of blood and blood components for transfusion. These procedures should include contingencies for shipping blood and blood components during an emergency prior to completion of required tests. Your SOPs concerning such medical emergency situations should be consistent not only with 21 CFR 610.40(g) as cited above, but also with the following:

- 21 CFR 606.151(e) - Procedures to expedite transfusion in life-threatening emergencies. Records of all incidents must be maintained, including complete

documentation justifying the emergency action, which must be signed by a physician.

- 21 CFR 606.160(b)(3)(v) - Appropriate records must be maintained, including, but not limited to, storage and distribution records in connection with the emergency release of blood, including the signature of the requesting physician obtained before or after release.

### **3. Staff Training**

In our November 2010 “Guidance for Industry: Recommendations for Blood Establishments: Training of Back-Up Personnel, Assessment of Blood Donor Suitability and Reporting Certain Changes to an Approved Application,” (Ref. 1) we recommend that blood establishments train personnel who may be called upon to assist in emergency response activities, including back-up personnel. We also recommend that establishments document their efforts in this area. Training may include participation in emergency preparedness training and exercises and instruction on roles and responsibilities in a severe local or national emergency.

### **4. Shipment of unlicensed products in interstate commerce**

FDA is aware that some blood establishments may be requested to ship unlicensed blood products interstate to support emergency blood needs. Consistent with FDA’s Compliance Policy Guide 220.100,<sup>2</sup> blood establishments that ship unlicensed products interstate in response to an emergency should maintain documentation relating to such incidents. FDA may request to review documentation in order to ensure emergency conditions exist and blood establishments are not improperly shipping unlicensed products between states.

### **5. Emergency-Related Variance Requests**

FDA has the authority to approve requests from blood establishments for exceptions or alternate procedures (variances) under 21 CFR 640.120 in areas impacted by disasters and emergencies, as was the case for blood centers impacted by Hurricanes Katrina and Rita. A list of FDA-approved variances is available on the CBER web site. <http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/RegulationoftheBloodSupply/ExceptionsandAlternativeProcedures/default.htm>

In a 2007 proposed rule<sup>3</sup>, FDA proposed to permit the Director of the Center for Biologics Evaluation and Research to issue an exception or alternative to the regulations in the event of a public health emergency. This procedure would be initiated only when a

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<sup>2</sup> IS Shipment of Biologicals for Medical Emergency, <http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm073860.htm>

<sup>3</sup> [Requirements for Human Blood and Blood Components Intended for Transfusion or for Further Manufacturing Use](http://www.fda.gov/BiologicsBloodVaccines/BloodBloodProducts/RegulationoftheBloodSupply/ExceptionsandAlternativeProcedures/default.htm)  
[http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=2007\\_register&docid=fr08no07-26.pdf](http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=2007_register&docid=fr08no07-26.pdf)

variance is necessary to assure the availability of blood, blood components, and blood products, in a specific location and in response to an unanticipated immediate need for blood, blood components, and blood products, as in situations involving large numbers of casualties.