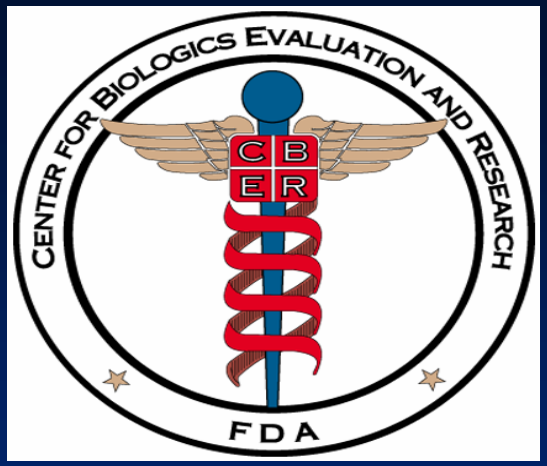

Regulatory Approaches to Preventing Blood Shortage Crises: Interventions, Triggers, and Pathways

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Key Characteristics of the US Blood Supply - System

- Unlike other developed nations, US does not have a national blood system
  - 45% American Red Cross (Single FDA license, 36 Regions)
  - 45% America's Blood Centers (78 independent, community blood centers)
  - 8% Hospital-based, and 2% DoD collections (DoD also contracts for blood with community blood centers)
- Most blood is stored at hospital transfusion services
  - Blood center inventory levels alone can be misleading
- The major blood organizations assert strongly that they have the ability to assess shortages and provide supply coverage in an emergency.
  - ARC monitors customer inventories
  - ABC loosely monitors member inventories (stoplight system)

Key Characteristics of the US Blood Supply - RBCs

- Approximately 50% of US RBC supply is estimated to be life-sustaining
- The remaining 50% of RBC transfusions are elective (some uses are poorly characterized)
  - Triage of available blood would be a powerful blood shortage intervention, but efforts to organize emergency triage beyond local levels have not been successful.
- Double RBC apheresis is a rapidly growing portion of RBC supply (30% of RBC collections at some centers.) Industry goal is to optimize apheresis components collected from each donor and reduce dependence on component laboratories (e.g. Group O RBCs + platelets; AB plasma + platelets)

Key Characteristics of the US Blood Supply - Platelets

- Platelet supply is vulnerable to sustained collection shortages
  - 5-7 day shelf life
  - Platelets, Pheresis now 85% of platelet supply and increasing
  - Ability to increase production of WB-derived platelets in emergency is limited (collection site distance and trend toward downsizing of component laboratories)
  - Off-hours Platelets, Pheresis collections could boost inventory ~50%

Key Characteristics of the US Blood Supply - Interdependencies

- Blood Availability is Dependent Upon a Complex Network
  - Donors
  - Trained Collection staff
  - Supplies
  - Test kits
  - Immunohematology Reagents
  - Centralized testing laboratories
  - Controlled storage facilities
  - Blood Establishment Computer Systems
  - Transportation

- Breakdown of any of these elements can lead to blood shortage.
- Blood shortages at the local level can (very quickly) become a safety issue.
  - Tribute to our current system that this has not happened

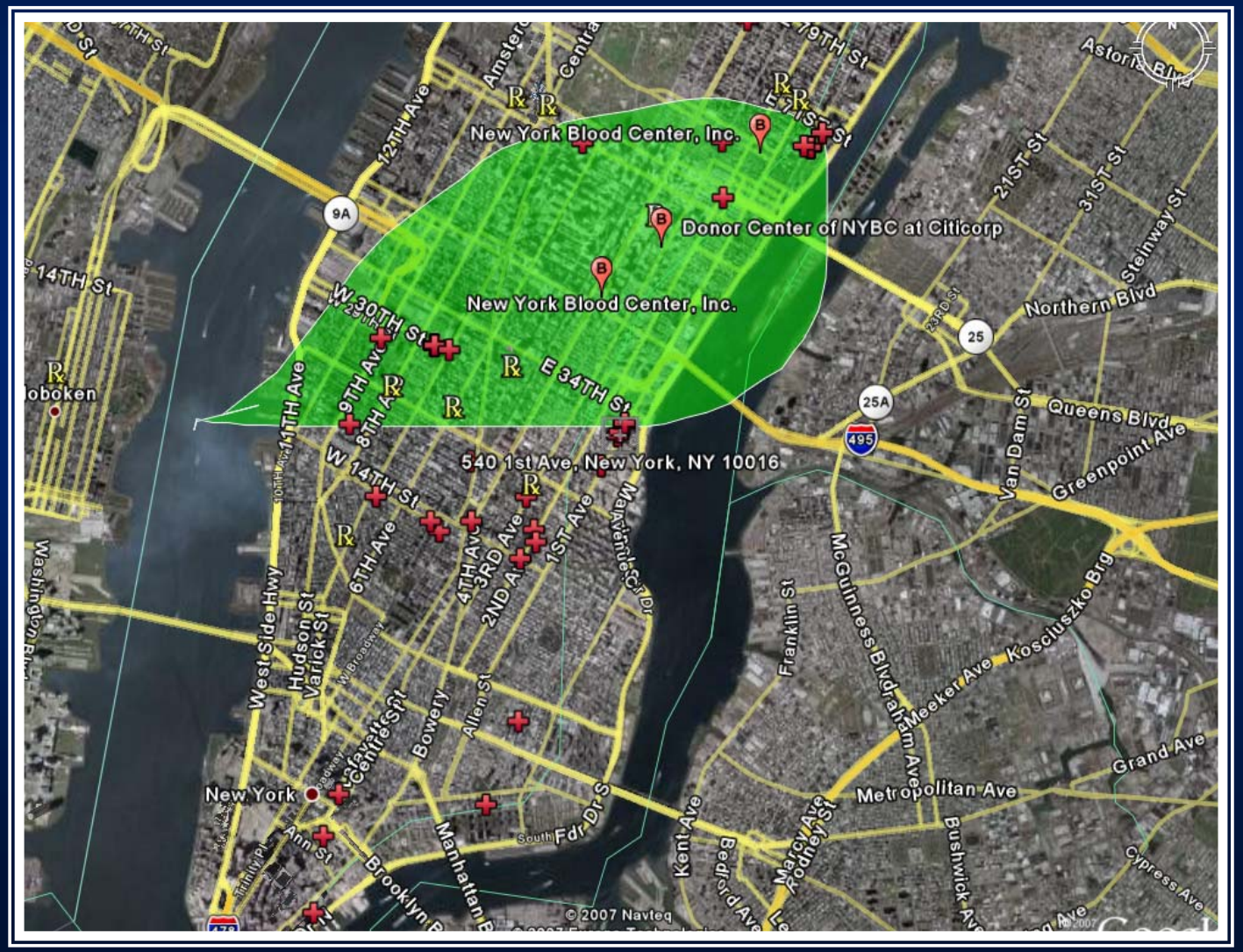
Key Characteristics of the US Blood Supply - FDA

- FDA has limited ability to influence the overall supply or movement of blood supplies
  - FDA can and does target safety interventions to preserve critical supplies
  - FDA has no control over production volume or distribution

- FDA Outreach
  - FDA has liaison to all AABB Disaster-Related Task Forces and Committees
  - FDA communicates and collaborates actively with PHS Agencies and DHHS
  - FDA has developed and shared TRANS-Net Blood shortage monitoring system design and provides Blood Establishment location databases and related GIS mapping utilities to DHHS.

GIS representation of Manhattan Blood Collection Facilities and a Hypothetical Path of Disruption

(CBER Blood Establishment Registration Database integrated with Google Earth Professional)



Existing Blood Supply Emergency Response Network

- AABB Interorganizational Disaster Task Force (TF)
  - Emergency blood supply coordination responsibilities under ESF-8 of NRP
  - Level 1 members and liaisons convene by telephone conference within one hour of an event (including representatives from affected blood establishments)
    - Level 1 participation includes all major blood organizations, HHS, FDA, CDC, DOD
    - TF has been active in TOPOFF exercises, as well as proactive planning for large events (political conventions, superbowl, etc)
    - Ability to monitor blood supplies down to local level for large-scale or sustained disaster is untested
- FDA recommendations are generally sought by the Disaster Task Force within hours of an event.

Interventions and Triggers

Pandemic Response Planning

Key Characteristics of the US Blood Supply – Pandemic planning

- AABB Pandemic Influenza Task Force
  - Proactive pandemic planning over past two years
  - Task Force has proposed FDA regulatory flexibility during pandemic-related shortages (Wide range of regulatory flexibilities proposed to FDA)
    - » Reduced interdonation intervals, supported by adequate hemoglobin or platelet count at intake
    - » Modified hemoglobin/hematocrit requirements
    - » Travel deferrals
    - » Weight limits, vital signs, other center SOP deferrals; some FDA required deferrals (like hepatitis after 11 years)
    - » Testing requirements of lower impact: WNV NAT, HIV/HCV NAT
    - » QC testing, audit timing, reporting requirements for BPDRs etc.
    - » Cross-training flexibility
    - » AABB has urged FDA to be transparent regarding its intentions so as to allow planning by the blood community
  - June 26 meeting with FDA liaisons

Pandemic Influenza: FDA positions conveyed to the blood community

- The best preparation is for Blood Establishments to anticipate pandemic-related disruptions and prepare back-up plans for key manufacturing steps (staff training, regulatory approvals, supply management, BECS override options, recordkeeping in an adverse environment)
- Surge collections early in recognized pandemic would help to maintain RBC supplies for first 6-8 weeks.
- Practice guidelines for triage of blood components used electively in times of emergency would greatly facilitate the optimal use of available blood supplies

FDA Regulatory “Flexibility” in a Time of Emergency

- FDA is committed to following its own statutes, regulations, guidances, and SOPPs
- Considerations of regulatory “flexibility” run counter to most of the measures that have been established to prevent deviations from established standards
  - Statutes (laws) - not flexible
  - Regulations - exceptions and alternatives via 640.120
  - Guidance - not required, but may be cGMP
  - Voluntary industry standards - not FDA required
- Emergency and Pandemic Response Issues are FDA-wide

FDA positions conveyed to the blood community - Modification of Standards

- Adherence to standards is a critical foundation of the current blood collection system.
- Any relaxation of standards will be dependent upon:
  - Recognition of shortages as an imminent public health threat
  - Supporting data that assesses risk:benefit to the greatest extent possible.
- At the same time, FDA is actively seeking mechanisms that will help to preserve critical blood supplies in a pandemic or other disaster (FDA flexibility was shown on 9/11/2001)

Specific Pandemic-Related Interventions Discussed at 6/26/2007 Meeting with AABB

1. Reduction of 56 day RBC interdonation interval based upon pre-donation Hb determination
   - projected large increase in RBC supply with minimal to no safety impact

2. Reduce weight requirements for double RBC apheresis by five pounds.

3. Relaxation of malaria and BSE-related travel deferrals (1-3% increase in accepted donors - establishments would not recruit deferred donors)

4. Relaxation of internal QC frequency and FDA reporting timelines

FDA positions conveyed to the blood community - Points to consider

The AABB-proposed regulatory “flexibilities” are a conceptual start, but are in need of more sophisticated assessment

1. What would be the gain in donors/donations?
2. What would be the impact on safety (donor and product)?
3. What organizational entity (community or government) would declare the need (and accept responsibility for) an intervention
4. From the blood establishment perspective, what mechanisms would produce the most efficient pathways for FDA to provide flexibility?

Walking Donor (WD) Programs

Walking Donor (WD) Programs

- WD concept not new, but FDA involvement grew out of June 13, 2007 Meeting with Boston Fresh Whole Blood Group.
  - Mass casualty event could exhaust local blood supplies (est 1000 pts x 5 units @)
  - 12-36 hours needed for blood supply re-mobilization (72 hours from collection)
  - 2-12 hours is critical period for trauma patient blood needs

Boston Proposal

- Identify cadre of recent blood donors (3-6 mos.) likely to be on-site
- Establish strict guidelines for transfusion of un-refrigerated Fresh Whole Blood (FWB)
  -(Note: Boston Group did not address authority for decision to use FWB)
- Administer abbreviated donor history questionnaire
- Blood would be untested at time of transfusion (rapid tests possible)
- Appropriate post-transfusion testing/follow-up

Walking Donor (WD) Programs

- FDA currently neither endorses nor dismisses the potential value of WD programs.

- Ideal characteristics
  - Group O donors with capability to rapidly express plasma
  - FWB blood collected/held under GMP by experienced blood collectors
  - Use of rapid tests for HIV, HBV, HCV

- Advantages
  - A sufficient supply of WD nationwide - combined with appropriate collection capabilities could address any blood shortage or crisis.
  - Donors interested in being WD would likely donate more frequently to retain WD status
  - Military has decades of experience with WD programs

Walking Donor (WD) Programs

- Hurdles
  - It remains to be determined whether WD programs have a unique niche that cannot be met by other supply mechanisms
  - Logistic hurdles of maintaining a viable WD program are huge
  - Current regulatory paradigm for blood precludes many aspects of WD program
  - Feasibility of Hospital vs Blood Center mobile WD collection sites

(Note: Use of WD mimics the risk from use of untested blood from repeat donors that would occur due to unavailability of donor screening tests)

Proposed Characteristics of Blood Shortages and Crises

Four types of blood shortages and CRISES for consideration

1. Shortage (large scale-extended)

2. Local CRISIS – (short-lived)

3. Large-scale CRISIS – (short-lived)

4. Large-scale CRISIS - (extended)

Shortage - “Don’t have it, can’t get it”

CRISIS = Imminent patient morbidity/mortality due to absence of blood

Four types of blood shortages and CRISES for consideration

1. Shortage (large scale-extended)

Example: Severe seasonal shortages

Frequency: 1-2/yr; national appeals @ 2-3 years

- Alternate supply sources
- Donation appeals

  Modified donor eligibility

  Modified Blood Establishment SOPs

  (Walking donor program)
- Transfusion triage

Four types of blood shortages and CRISES for consideration

2. Local CRISIS – (short-lived)

Example: Severe trauma or BT/CT event – local supplies exhausted
Frequency: Anticipated on 9/11/2001, but never observed in US

- Alternate supply sources (subject to transportation time lag)
  - Donation appeals
  - Modified donor eligibility
- Modified Blood Establishment SOPs

- (Walking donor program)
- Transfusion triage

9/11/2001

- Mid-day reports indicated a potential for thousands of severe traumatic injuries in NYC and Washington, D.C.

- FDA issued same-day guidance
  - Provisions for training and certification of emergency staff members
  - Release and use of units that are not fully tested. To be labeled “For emergency Use Only” with list of tests not completed
  - Enforcement discretion for interstate shipment by registered-only facilities with label “Unlicensed, For Emergency Use Only”
  - Product Identification and Record-keeping

9/14/2001

- By 9/14 it was evident that extra blood was not needed for attack victims

- FDA issued revised recommendations
  - Discontinuation of collection by emergency trained staff
  - Quality assurance investigation reported to FDA within 72 hours.
  - Discontinue any use of untested units (exc. where NAT still unavailable)

Post-9/11 Lessons

- Quality assurance assessments indicated that much of the blood collected under emergency conditions was not suitable for inclusion in the non-emergency community supply
- Identified need for consistent public messaging regarding adequacy and safety of the blood safety, need for interested donors to schedule future donations
- Led to formation of the AABB Interorganizational Task Force on Disasters

Four types of blood shortages and CRISES for consideration

3. Large-scale CRISIS – (short-lived)

Example: Multi-focal BT/CT event; critical supply disruption
Frequency: Never observed in US

- Alternate supply sources (subject to availability, time lag)
  Donation appeals (donor shortages not the problem)
  Modified donor eligibility (donor shortages not the problem)
- Modified Blood Establishment SOPs
  (Walking donor program)
- Transfusion triage

Four types of blood shortages and CRISES for consideration

4. Large-scale CRISIS - (extended)

Example: Severe pandemic

Frequency: Never observed in US

Alternate supply sources (unlikely to be available)

- Donation appeals (subject to willingness of donors to appear and blood center staffing)
- Modified donor eligibility
- Modified Blood Establishment SOPs
- (Walking donor program)
- Transfusion triage

Interventions, Triggers, and Pathways

Current Status

Regulatory Approaches to Preventing Blood Shortage Crises: Interventions, Triggers, and Pathways

Step I. Define candidate interventions – including risk/benefit assessments

- As a result of collaborative pandemic influenza planning, candidate interventions appear to be coming into focus and are at the stage of risk:benefit analysis.(Including models of blood supply dynamics being developed at CBER.)

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Step II. Define appropriate triggers

- Triggers for response largely remain undefined - including levels at which implementation decisions will be made, who bears responsibility, role of public vs. private sector
- Discussion of useful intervention triggers with AABB Pandemic TF was not conclusive
- Inventory figures are difficult to interpret
- As proposed in the FDA TRANS-Net Program, the best trigger for interventions may the "impact" of blood shortages at the local transfusion service level.
  - Cancelled elective surgery
  - Rh+ blood to Rh- patients
  - Transfusion Triage
  - Imminent patient morbidity/mortality
- (Note: Transfusion services measures were deemed unreliable by the AABB Pandemic Influenza TF)

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Step III. Consider FDA regulatory pathways appropriate to the situation

- ✓ Strongly encourage proactive contingency planning by regulated manufacturers
  - Modified Regulations
  - 640.120 Exceptions and Alternate Procedures
  - Issue new guidance
  - Enforcement Discretion
  - Interstate shipment of Blood Products for Medical Emergencies
  - IND
  - EUA

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Step IV. Plan realistically

- There is general agreement about the value of proactive planning regarding measures to sustain the blood supply in the face of a disaster.

- There should be caution in basing these plans solely upon the parameters of past disasters with no contingency plan for larger-scale events (not yet experienced) that may cause severe disruptions to the fragile blood supply chain on multiple levels at numerous locations.