FDA's Safety Surveillance System for Blood and Blood Products

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for presentation to the
Advisory Committee on Blood Safety and Availability
May 16, 2005
Bethesda, Maryland

Blood Safety Assurance and Surveillance

- Encompasses protection of blood (including components and products), donors, and recipients
- Multiple interconnected and overlapping safety domains and reporting systems
  - Deaths: donors, recipients
  - Product failures (“errors and accidents”)
  - Device malfunctions
  - Adverse events (AE’s) in product recipients
  - Medical errors

How are Donors Protected?

- Confidential interview
- Health screen
- Rapid access to emergency care
- Notification of donors with medical referrals upon deferral for abnormal findings, including infectious disease test results

How is Blood Made Safe?

Five Layers of Blood Safety

1. Selection of suitable donors
   - Donor education
   - Extensive risk factor screens (including malaria and vCJD)
   - Limited physical examination
2. Use of deferral registries to identify unsuitable donors
3. Infectious disease testing (HIV-1, HIV-2, HCV, HBV, HTLV-I HTLV-II, syphilis, CMV)
4. Blood quarantine pending tests and suitability determination
5. Monitoring, investigating, and corrective actions for errors, accidents, and adverse reactions

cGMP's and product standards apply in all areas

– Staff training and certification; SOP's; Use of approved methods

– Pathogen reduction for plasma derivatives

– Bacterial contamination monitoring

How are Recipients Protected ?

- Safe blood (including components and products) assured through 5 blood safety layers and cGMP's
- Automated processes reduce human errors
- Blood and components are grouped and crossmatched for compatibility with recipient
- Other safety systems include:
  - Recipient, sample, and unit identifiers
  - Hospital practice standards
  - Event investigation and reporting
  - Corrective actions

Blood Safety Event Reporting

- **Mandatory:** reporting by manufacturers
  - Fatalities (donors and product recipients)
  - Product failures (errors and accidents)
    - Biological Product Deviation Reports
    - Medical Device Reports
    - Adverse events*
- **Voluntary:** "spontaneous" adverse event reporting to FDA AERS (MedWatch) from any source
- **Medical errors:** primarily reported through the hospital system, rather than to FDA

*Currently excluding manufacturers of blood and blood components

Blood Fatality Surveillance for Transfusions and Donations

- When a blood donor or recipient dies
- With possible relationship to the donation or transfusion
- Blood collecting or transfusing facility must notify CBER's Office of Compliance and Biologics Quality (OCBQ)

Leading Fatality Categories*

Transfusion-Related Acute Lung Injury (TRALI) (reporting likely stimulated by 10/2001 FDA Health Alert)	20.1%
ABO and other hemolytic transfusion reactions	13.9%
Bacterial contaminations	11.9%

*data from FY 2001-2004; less frequent categories include infections, clear or possible non-transfusion causes, and donor deaths

Bacterial Contamination

- Rarely implicated in deaths but frequently reported as “product deviations”
- Special concern for platelets, due to room temperature storage and utilization before reliable culture results may become available
- Potential Sources
  - Donor bacteremia, asymptomatic or following a medical procedure
  - Inadequate skin disinfection
  - Skin coring
  - Contaminated apheresis solution water baths, pack exteriors, or failed sterile connections

Biological Product Deviation (BPD) Reporting Objectives

- Early warning system
  - for possible problems in advance of scheduled inspections (generally every 2 years)
  - Indicator of potential immediate problems or need for a product or lot recall or prompt “directed inspection”
- Surveillance
  - Training for investigators and industry
  - Guidance for investigators before and during inspections, and for development of guidance documents and policies for industry

BPD: Who Must Report?

- Licensed manufacturers of blood and blood components, including Source Plasma
- Unlicensed registered blood establishments
- Transfusion services

BPD: What is Reportable?

Any event associated with manufacturing of blood or blood components (licensed or unlicensed) that:

- Deviates from cGMP, regulations, standards, or specifications that may affect safety, purity, or potency;
  or
- Is unexpected or unforeseeable and may affect safety, purity, or potency;

  and
- Involves a distributed biological product

BPD Reports*

Donor Suitability (usually post-donation information)	76.5%
Quality control and distribution	9.9%
Labeling	6.4%
Testing	3.0%
Collection	2.2%
Component preparation	1.0%
Miscellaneous	1.0%

*among 37,830 reports received in FY-2004

Medical Device Reporting

- **Requirement:** Manufacturers must report a device-related death, serious injury, or malfunction within 30 days
- **In-Vitro Diagnostics**
  - Viral Marker test kits – e.g., HIV, Hepatitis
  - Blood Bank reagents – e.g., ABO/Rh, antibody screening
- **Devices**
  - Apheresis collection devices
  - Hematology analyzers for donor testing
  - Bacterial Detection Systems to test blood and components
- **Computer Software:** blood bank programs that can give incorrect results through inadequate design and/or validation

Adverse Event Monitoring and Reporting

- **AERS/MedWatch:** FDA safety information and reporting program
- Receives mandatory reports from manufacturers
- Receives voluntary reports from anyone
- Multiple submission modalities:
  - online for individuals
  - batch electronic submissions from manufacturers
  - Telephone
  - Fax
  - mail

Non-Fatal AE Reports Not Required for Blood and Blood Components

- Blood collection and transfusion facilities
  - currently required to conduct investigations and maintain reports of all AEs associated either with the collection or transfusion of blood or blood components.
  - reports reviewed during FDA establishment inspections, at least every 2 years
  - submission to AERS/ MedWatch not required
- A proposed rule would change these requirements.

Proposed Reporting for Blood and Components: Serious Non-Fatal AE's

Safety Reporting Requirements for Human Drug and Biological Products Proposed Rule (Federal Register, March 14, 2003)

- Obligation to report:
  - Facility performing compatibility testing for AE related to transfusion
  - Collecting facility for AE related to the blood collection procedure
- Written report
- To FDA Center for Biologics Evaluation and Research
- Within 45 calendar days

Surveillance System Strengths

- Anyone can report
- Confidentiality for reporters and patients
- Non-punitive to avoid reporting disincentives
- Open-ended to allow detection of unanticipated problems
- National scope
- Capabilities for rapid recognition of issues and appropriate responses to
  - Assess tentative signals
  - Control verified problems
  - Learn from experience

Surveillance System Limitations

- Fragmented reporting systems
- Passive surveillance
  - Under-reporting pervasive in voluntary systems
  - Biases and confounding factors often require consideration
- AE reports in AERS may be causally or only coincidentally related to the product
- Spontaneous reports are often incomplete
- No control groups
- Frequently lack denominators

Summary

- Blood safety depends on multiple, overlapping systems at every stage from assessing donors to identifying recipients.
- Important limitations include fragmentation of systems and incompleteness of event ascertainment, particularly for voluntary reporting systems.
- Strengthened reporting requirements for serious adverse events may improve blood safety surveillance in the near future.

Acknowledgments

Jay S. Epstein, MD	OBRR
Leslie Holness, MD	OBRR
Sharon O'Callaghan, MT(ASCP)	OCBQ
Lois Simmons, MT(ASCP)	OCBQ
Kathryn O'Connell, MD, PhD	OBE
Ann R. Gaines, PhD, MT(ASCP)	OBE