Safety Surveillance for Licensed Biological Products at FDA's Center for Biologics Evaluation and Research

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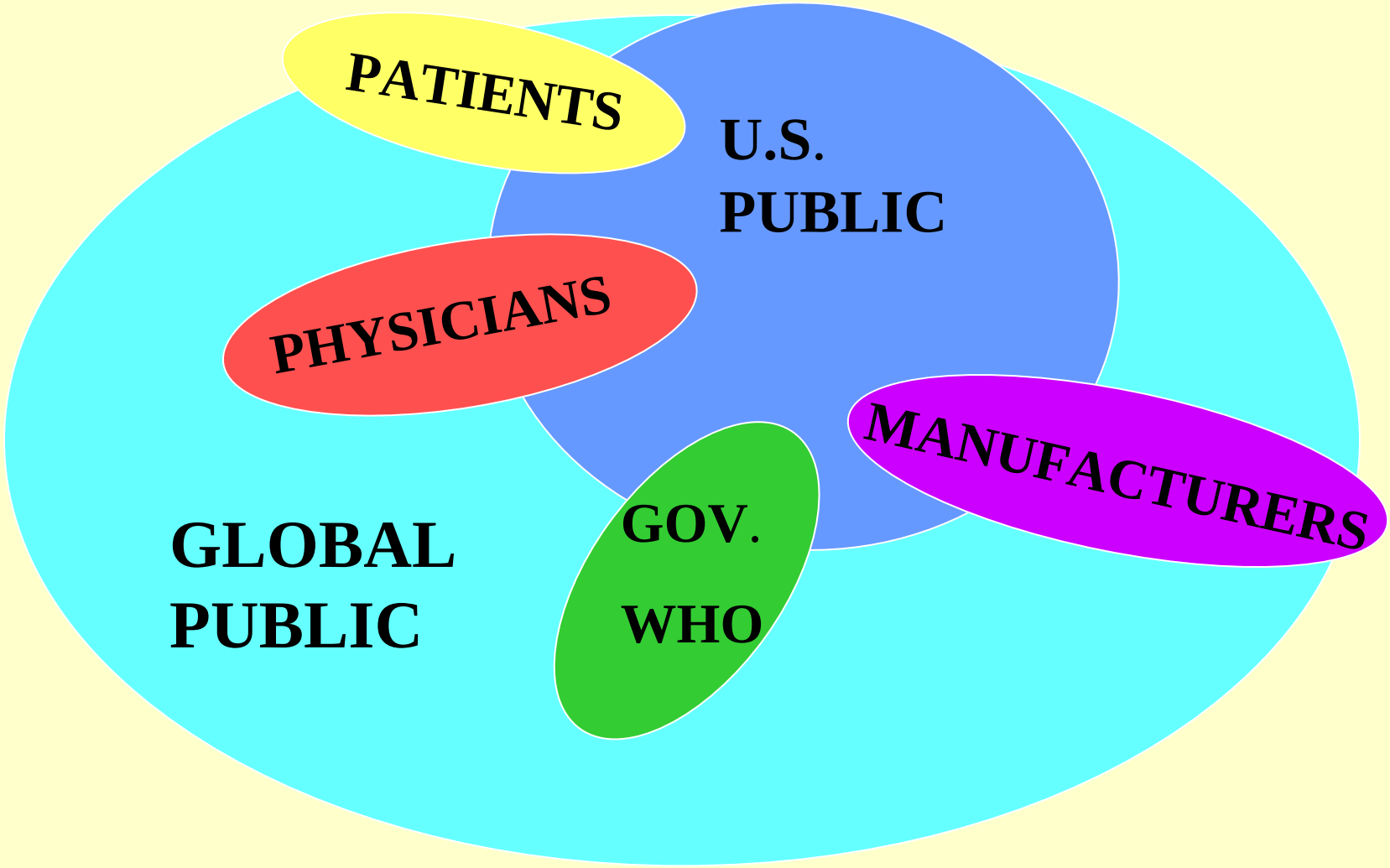
The speaker's views may not reflect official FDA policies or positions.

Post-Market Surveillance (PMS) at CBER

- Goals and principles
- Biological products
  - Tissues and cells
  - Vaccines
  - Blood and blood products

Many partners share responsibilities for safety surveillance after product marketing begins!



CBER Assures Safety and Efficacy of Licensed or Regulated Products

- Vaccines, toxins, antitoxins
- Blood, components, and derivatives
- Allergenic extracts
- Human tissue products (only safety)
- Human cellular products
- Devices involving biological products
- Xenotransplants
- Future: Gene therapies

Biologicals vs. Drugs

- Biologicals traditionally prophylactic
  - administered to healthy persons for threats of future illnesses
  - frequently given to most of population
  - require very high benefit/risk ratio
- Drugs typically therapeutic
  - given to ill patients
  - Substantial serious risks frequently acceptable in consideration of anticipated therapeutic benefits
- But this distinction is waning:
  - Most vaccines are still preventive and require exceptional benefit/risk ratios
  - But many therapeutic biologicals (e.g., specific immune globulins or BCG for bladder cancer) can provoke substantial but acceptable morbidity.

Post-Licensure Safety Surveillance for Biologicals vs. Drugs

- Philosophies and methods generally similar
- Numerous variables in biological production processes
  - Contrast with precise, chemically-defined composition of traditional small molecule drug products;
  - After licensure, CBER continues to “release” product lots, maintains lot distribution database, and monitors AE reports for possible lot-specific patterns.

Historical Biological Safety Incidents

- **Lot-specific**
  - 1901: Contaminated diphtheria antitoxin lot; 13 fatal tetanus infections
  - 1955: "Cutter incident" 204 vaccinee or contact poliomyelitis infections from new Salk vaccine with deficient viral inactivation (7 lots)
  - 1996: Septic shock during albumin infusions led to recognition that Enterobacter cloacae had contaminated at least one lot.
- **Others**
  - 1970's: Hemophiliacs and others developed AIDS from contaminated units of whole blood, cellular components, and plasma derivatives until effective procedures to restrict donors and test donations became available.
  - 1958-1985: Creutzfeldt-Jakob Disease from human pituitaries
  - Intussusception after first rotavirus vaccine

FDA does not regulate the "practice of medicine."

- Off-label use of licensed products is legal and can be medically sound.
- Safety surveillance encompasses all product use, including patient experiences with unlabeled indications.

CBER'S Role and Goals in Safety Surveillance

- Work with manufacturers to assess need for pharmacovigilance plans and other Phase 4 studies; often assist with design and review results.
- But most additions to safety data after licensure stem from spontaneous reports of suspected side effects.
- Several safety surveillance objectives:
  - **Detect new risks** (previously unrecognized reactions, including medication errors).
  - **Identify new information about known risks**, such as greater rate or severity or specificity than previously appreciated, including infection surveillance.
  - Look for pertinent pre-existing conditions to **find risk factors** that might guide future prescribing for safer use of products.
  - Monitor patterns by production lot.

Passive Surveillance: Pro and Con

- STRENGTHS:
  - Open-ended for hypothesis generation
  - Potential detection of new or rare adverse events
  - Timeliness
  - Geographic diversity
  - Capability to monitor production lots
- LIMITATIONS:
  - Missing and inaccurate data
  - Under-reporting
  - Absence of controls and denominators
  - Inability to assess causation
  - Low likelihood of detection for long latency events

Passive Safety Surveillance Systems

- Current
  - **Vaccine Adverse Event Reporting System** (**VAERS**)
    - Jointly operated by FDA and CDC since July 1990
    - Approximately 12,000 reports annually, 15% serious
  - **Adverse Event Reporting System** (**AERS**/MedWatch)
    - Pre-VAERS private sector vaccine reports
    - Includes indications since 11/1997
- Previous
  - FDA Spontaneous Reporting System (**SRS**)
  - CDC Monitoring System for Adverse Events Following Immunizations (**MSAEFI**)
    - Pre-VAERS public sector vaccine reports
    - “Check box” format

FDA's Safety Surveillance for

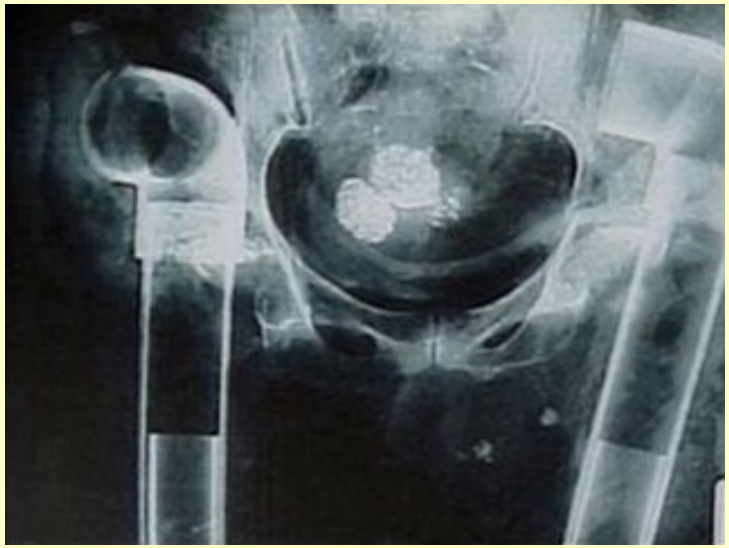
Human Tissue and Cell Products

Tissue and Cell Safety Surveillance

- Products not licensed
- Regulatory framework differs from that for drugs and most biologicals
- Based on **FDA authority to control transmission of infectious disease**
- Hence primary current focus on allograft-attributable infections from
  - contaminated donor (cadaveric or living) cells and tissue or
  - contamination through processing
- CBER frequently collaborates with CDC

Problems with donor eligibility evaluations in BTS and DRS tissue recovery operations

- Falsification of causes of death on death certificates
- Substitution of blood samples for infectious disease testing from persons other than the identified donor



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FDA/CDC Responses

- Prompt recognition of threat to tissue safety
- Formation of Human Tissue Task Force "to strengthen [FDA's] comprehensive, risk-based system for regulating human cells and tissue." (http://www.fda.gov/bbs/topics/NEWS/2006/NEW01440.html)
- Public Health Notifications to inform physicians and encourage tissue recipients to be tested for potentially transmitted diseases
  - http://www.fda.gov/bbs/topics/NEWS/2005/NEW01249.html
  - http://www.fda.gov/cber/safety/bts030206.htm
  - http://www.fda.gov/Cber/safety/drs083006.htm
- Publication: *Investigation into Recalled Human Tissue for Transplantation - United States, 2005-2006.* MMWR. 2006;55:564-566

FDA's Safety Surveillance for

Vaccine Products

VAERS

- National Childhood Vaccine Injury Act (NCVIA) requires manufacturers and physicians to report certain adverse events after specified vaccinations within particular time frames.
  - But VAERS centralizes surveillance by accepting reports from anyone for any adverse event after any vaccine.
  - Essential character of surveillance remains passive, voluntary, “spontaneous”
- Collaborative: FDA, CDC, vaccine manufacturers, and reporters (physicians, patients, parents, and others)
- http://www.vaers.org; 1-800-822-7967

Vaccine Safety Example

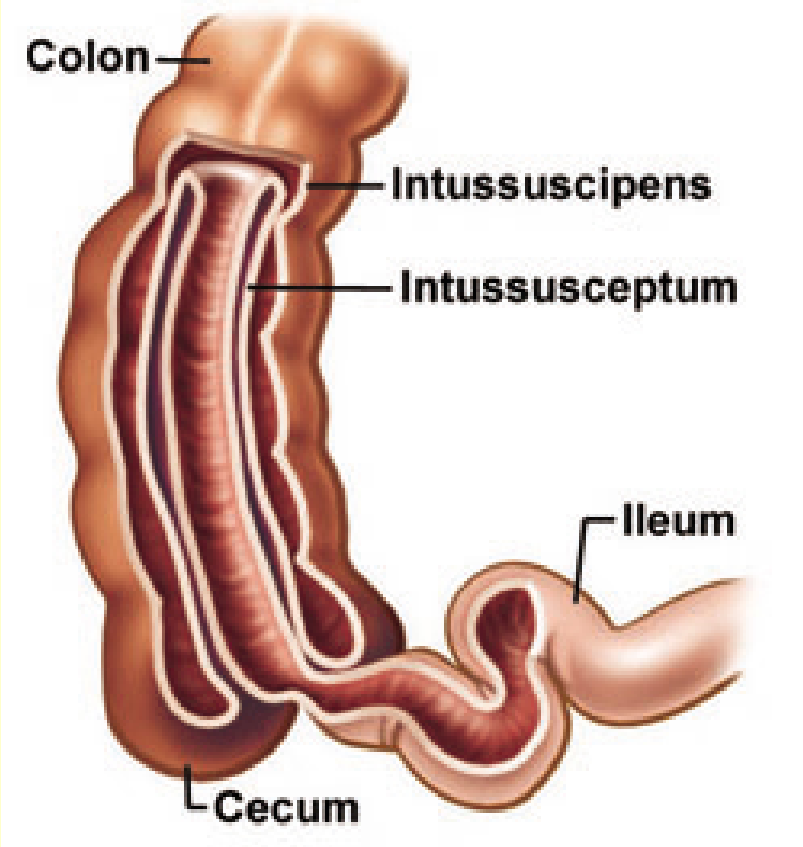
Rotavirus Vaccine and Intussusception

Paradigmatic Illustration of Successful Surveillance

Rotavirus Diarrhea

- Kills millions (mostly infants, toddlers) in developing world; rarely fatal in U.S.
- **August, 1998:** FDA licensed the first live virus rotavirus vaccine (RV), with primary public health hope to help infants in the third world.
- **Patients in clinical trials had developed intussusception**
  - 5 cases among 10,054 vaccinees
  - 1 case among 4,633 controls
  - Relative risk 2.3, “not significant”

Intussusception: invagination of an infant's intestine



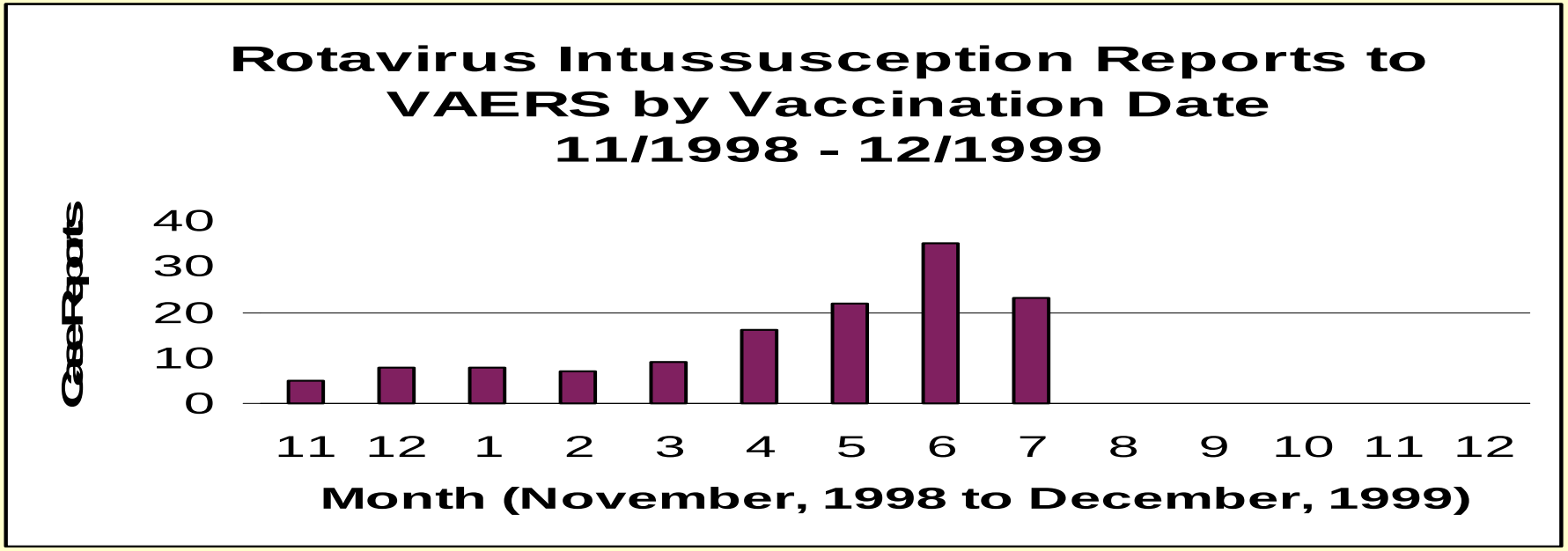
http://www.yoursurgery.com/procedures/intussusception/images/Intussusception.jpg

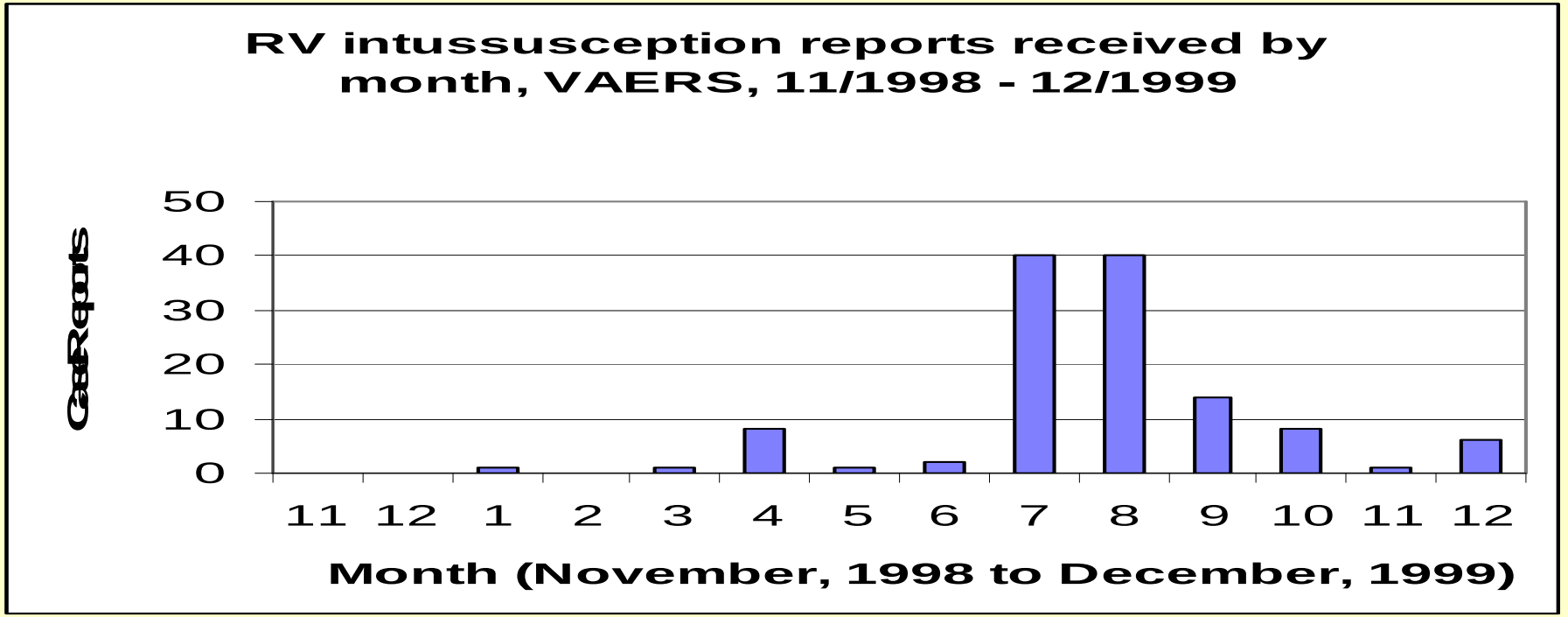
Intussusception Background

- Etiology unknown; peaks at ages 4-6 months
- Obstructs and kills unless recognized and treated
- Diagnostic radiology (barium or air contrast enema) often curative
- Otherwise resection of necrosed intestinal segment imposes
  - acute risks from anesthesia and major abdominal surgery
  - long term risk of short bowel syndrome

Case Reports after RV Licensure

- 11 reports received by **6/1/1999**
- CDC calculations suggested similar number expected in a population of size and age vaccinated.
- But with under-reporting, actual post-vaccinal numbers could be much larger.
- **7/1999:** RV use suspended pending urgent epidemiologic studies


Rotavirus Intussusception Reports to VAERS by Vaccination Date 11/1998 - 12/1999
Case Reports
40
30
20
10
0
11 12 1 2 3 4 5 6 7 8 9 10 11 12
Month (November, 1998 to December, 1999)


RV intussusception reports received by month, VAERS, 11/1998 - 12/1999
Case Reports
50
40
30
20
10
0
11 12 1 2 3 4 5 6 7 8 9 10 11 12
Month (November, 1998 to December, 1999)

RV-Intussusception Lessons

- Profound product hazard clearly appreciated only after licensure, despite hints from Phase 3 study
- Risk management required product withdrawal
- Rare quantitative evidence of
  - initial **under-reporting** followed by
  - **publicity stimulation** of reporting

FDA's Safety Surveillance for

Blood and Blood Products

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 status evaluations
- 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
  - Recently implemented bar codes
  - Radio Frequency Identification (RFID) tags on horizon
- Blood and components are grouped, typed, 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 Reporting

- **Mandatory:** reporting by manufacturers
  - Fatalities (donors and product recipients)
  - Product failures (errors and accidents)
    - Biological Product Deviation Reports
    - Medical Device Reports
  - Other adverse events*
- **Voluntary:** "spontaneous" reporting to FDA's Adverse Event Reporting System (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 from
- "a complication of donation or transfusion"
- Blood collecting or transfusing facility* must notify CBER's Office of Compliance and Biologics Quality (OCBQ)

*that performed type and cross-match

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 (no inter-state commerce)
- 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

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

rFVIIa and Thromboembolic Events

- Recombinant factor VII activated (rFVIIa, NovoSeven) licensed “for the treatment of bleeding episodes in hemophilia A or B patients with inhibitors to Factor VIII or Factor IX”
- Increasingly used off label for non-hemophiliacs
  - Case reports to FDA describe a variety of arterial and venous thromboses in 17 hemophiliacs and 151 other patients.
  - Major safety concern in published literature is thrombotic risk in patients without hemophilia.
- rFVIIa generates more thrombin in vitro with normal blood than with hemophiliac blood.
- Formation of undesired thrombus likely also depends on vasculopathy (exposing tissue factor), but it seems plausible that rFVIIa’s safety could differ between hemophiliacs and normal patients.
- Because most cases also have other possible causes, only controlled clinical trials of rFVIIa for additional indications will clarify its safety and efficacy for non-hemophiliacs.

CBER Safety Summary

- Diversity of biological products requires multiple surveillance and safety assurance strategies.
- Open-ended safety surveillance essential for earliest possible discovery of unanticipated hazards to the public health.