

# Safety-Related Impurities in Plasma-Derived Products

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CDER Small Business & Industry Assistance (SBIA)  
Regulatory Education for Industry (REdI) Annual Conference  
June 6-10, 2022



# Learning Objectives

- Describe examples of impactful investigations into unexpected serious adverse events caused by impurities and contaminants in plasma-derived products
- Discuss
  - manufacturing root causes and
  - mitigation strategies

## Disclaimer



My comments are an informal communication and represent my own best judgment. These comments do not bind or obligate FDA.

# Plasma-derived products

- Human blood plasma is a complex biological fluid rich in proteins, carbohydrates and lipids
- Examples of plasma-derived products:
  - Immune globulins: normal and hyperimmune
  - Albumin
  - Coagulation (clotting) factors
  - Topical hemostasis: fibrin glue, thrombin spray

# Impurities in biological products



- Complete removal of process- and product-related impurities is impossible
- Impurities are potential Critical Quality Attributes (CQAs) because of their potential impact on product safety (ICH Q11)
- Control strategy should consider both manufacturing feasibility and safety risks
- Fortunately, cases of product safety impact are rare

# Impurities in plasma-derived products



- Plasma components can co-purify with target proteins
- Select few impurities and contaminants were associated with clusters of serious adverse events:
  - Hypotension
  - Viral transmission
  - Bleeding
  - Thrombosis



1977

# Hypotension

# Plasma protein fraction (PPF)

- Available since 1950s: 21 CFR Part 640, I
- Protein fraction comprised of 85% pure albumin and heat-treated to inactivate Hepatitis B virus
- Widely used in 1950s-1980s as colloid volume expander
- Given in critical blood loss situations to avert hypotension (no solid evidence of benefit vs. crystalloids)



# Serious adverse event: hypotension



- In early 1977: reports of severe hypotension AEs



# PreKallikrein Activator (PKA) impurity



66

THE NEW ENGLAND JOURNAL OF MEDICINE

July 13, 1978

## **HYPOTENSION ASSOCIATED WITH PREKALLIKREIN ACTIVATOR (HAGEMAN-FACTOR FRAGMENTS) IN PLASMA PROTEIN FRACTION**

BARBARA M. ALVING, M.D., YOSHIO HOJIMA, PH.D., JOHN J. PISANO, PH.D., BOBBY L. MASON, M.S.,  
RICHARD E. BUCKINGHAM, JR., M.D., MILTON M. MOZEN, PH.D., AND J. S. FINLAYSON, PH.D.

- “Thirteen lots of plasma protein fraction made by one manufacturer were implicated in 23 recent reports of hypotension in surgical patients”
- All implicated lots had PKA activity:
  - 9 ng/mL can cause a hypotensive episode
  - 25 ng/mL can cause total circulatory collapse

# Long-lasting mitigation strategy



## History

of the

U.S. Food and Drug Administration

Interviewee: John S. Finlayson, Ph.D.

Interviewer: John P. Swann, Ph.D.  
Robert A. Tucker

Date: June 11, 2009

Place: Rockville, MD

- “The big recall happened in late May or early June of 1977”: 1.2 million grams of protein or **25 kilotons** of product was recalled”
- Release limits on PKA now exist for albumin, PPF, and immune globulins products

1982

# **Viral transmission**

# Viruses in factor concentrates

- Life expectancy of hemophilia patients (deficiency of a coagulation factor) increased from ~10 years in early 1900s to ~70 years during 1971–1980
- In 1982, factor concentrates, prepared from large plasma pools, were identified as the source of AIDS infections of hemophilia patients
- In just 2 years, 60% of the U.S. hemophilia patients were infected with HIV via concentrates, with life expectancy dropping to 40 years during 1981-1990

# Viral transmission mitigation

- Today, risk of viral transmission by pooled plasma-derived products is effectively mitigated via
  - Qualification of plasma donors
  - Use of reliable viral tests for individual donations and pools
  - Orthogonal viral inactivation and reduction process steps
- “**Contaminants** in a product include all adventitiously introduced materials not intended to be part of the manufacturing process” <sup>1</sup>



1989

# Bleeding



# Topical bovine thrombin

- Protease thrombin converts soluble fibrinogen into fibrin clot
- Bovine-derived topical thrombin used as an adjunct to surgical hemostasis since 1940s; FDA approved since 1970s
- Since 1989, reports of acquired bleeding conditions were linked to product exposure during surgery



# Root cause: bovine Factor V impurity



- Adverse events included impaired wound repair associated with thrombosis, uncontrolled bleeding, shock, or death
- Root-cause: patient's anti-bovine Factor V antibodies cross-react with human Factor V
- Manufacturing processes were developed to reduce bovine Factor V impurities
- Risk of adverse events is substantially mitigated



2010

# Thrombosis

# Immune Globulin, Intravenous (IGIV)



- Immune globulin G - available since 1940s (1981: i.v. product)
- Manufactured from pooled plasma of 7,000 – 60,000 donors
- Numerous indications: immune deficiencies, Kawasaki syndrome, various neurological, blood, rheumatic, skin, and many other diseases

# Thrombotic adverse events

- First literature report in 1986
- ~30 events per year (spontaneous reporting, 1999-2005): myocardial infarction, stroke, deep venous thrombosis, and pulmonary embolism
- Precautionary labeling recommended by FDA since 2003
- Back then, causes remained uncertain

# **“Clusters” of adverse events**

- In 2010, manufacturer reported thrombotic events clustered with 2 product lots
- FDA laboratory found elevated coagulation Factor Xla impurity and proposed detection method
- Manufacturer confirmed results and initiated lot withdrawal
- 2010-2012: Industry-wide evaluation of impurities and adverse events

# Product recalls in 2010-2012

**URGENT: Voluntary Market Withdrawal - September 23, 2010**  
**Octagam [Immune Globulin Intravenous (Human)] 5% Liquid Preparation**

DATE MARKET WITHDRAWAL INITIATED:  
 September 23, 2010

## URGENT VOLUNTARY PRODUCT RECALL

Omr-IgG-am™ 5% IV, Registration Number 127543069800 - ALL LOTS

**Important Safety Information: Risk of Thrombotic Adverse Events with Subcutaneous or Inappropriate Intravenous Use of Vivaglobin (Immune Globulin Subcutaneous)**

**IMPORTANT SAFETY INFORMATION: Potential Risk of Thrombotic Events with Use of GamaSTAN® S/D (Immune Globulin (Human))**

May 29, 2012

Please be advised that Cangene Corporation is issuing a voluntary **DRUG RECALL** of the following finished product lots associated with one bulk lot of the following product:

### **Product Name/Description:**

Hepatitis B Immune Globulin (Human) (HepaGam B) (> 312 IU/mL)

**Theoretical Risk of Thrombotic Events with Intravenous HepaGam B® (Hepatitis B Immune Globulin (Human) Injection) and Related Labeling Update**

June 11, 2012

# Mitigation strategies

- To address safety concerns, manufacturers of investigational and licensed products agreed to introduce
  - Manufacturing changes to reduce Factor Xla
  - Lot release testing to control Factor Xla
- Work on harmonization of release testing methods and limits is ongoing

# Ongoing international collaboration



2011 FDA-PPTA-HHS Public workshop on risk mitigation

2012, 2014 WHO international standards for Factor Xla activity

2014 EMA-EDQM meeting on establishment of common test

2016 PPTA Stakeholder forum on methods

2016-2022 FDA-NIBSC-USP-EDQM Global Working Group on methods



# Challenge Question #1

**Which of the following is a contaminant?**

- A. PKA enzyme
- B. HIV
- C. Factor V fragments
- D. Factor Xla enzyme

## Challenge Question #2

**Which of the impurities or contaminants were not expected to come from plasma?**

- A. Coagulation enzymes: PKA and FXIa
- B. Bovine Factor V fragments
- C. Viruses
- D. None (i.e., all were theoretically possible)

# Summary



- Plasma-derived impurities and contaminants have caused severe adverse events
- Post-event mitigation strategies can be burdensome:
  - Product recalls
  - New process steps
  - New in-process and release testing
- Severe adverse events were caused by theoretically known although not (yet) controlled impurities

# Closing Thought

Sponsors should consider relevant  
*product-specific* impurities &  
contaminants and possible safety risks