

FDA Considerations Regarding Frequent Plasma Collection Procedures

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15th International Haemovigilance Seminar
Brussels, Belgium
January 20-22, 2013



Acknowledgements

- Les Holness, MD (Retired)
Chief, CBER¹, OBRR² Blood and Plasma Branch
- CBER fatality review committee
- OBRR, OBE³ and OCBQ⁴ staff.
 1. Center for Biologics Evaluation and Research
 2. CBER Office of Blood Research and Review
 3. CBER Office of Biostatistics and Epidemiology
 4. CBER Office of Biologics Compliance and Quality
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Safety of Blood and Plasma Donation

- All evidence to date strongly supports a very high level of safety for blood and plasma donation in the United States.
- Fatalities following blood and plasma donation are reported to FDA. The data suggest that these events are very rare.
- A previous analysis (2003 BPAC) failed to demonstrate excess fatalities compared with predicted actuarial rates, or causality related to donation.

Safety of Blood and Plasma Donation (cont.)

- FDA periodically revisits summary donor fatality data, in particular when there are apparent upticks in the number of reported fatalities.
- An elevated Body Mass Index (BMI >30) and cardiovascular events continue to be observed in association with reported fatality cases.
- FDA is actively pursuing further controlled investigation of BMI and any other predictive co-factors that may exist.

Source Plasma Donor Selection Criteria (Medical History and Examination)

- Performed by trained persons supervised by a qualified licensed physician
- Physical examination and informed consent (initially and annually)
- Donor questionnaire includes questions about general health and past medical history

“Have you EVER had any problem with your heart or lungs?”

- Freedom from any disease, other than malaria, transmissible by blood transfusion

Donor Selection Criteria: Physical Examination (640.63)

- Weight 110 lb. or more (no upper limit)
- Temperature $\leq 99.5\text{F}$ (37.5C) *
- B. P. systolic/diastolic (90-180/50-100) *
- Pulse 50-100 bpm *
- Hemoglobin ≥ 12.5 g/dL
- Hematocrit $\geq 38\%$
- Total protein ≥ 6.0 g/dL at each donation
- Normal SPE verified every 4 months

**Industry standard*

US Source Plasma Donation Intervals

- Not more than two donations/week for frequent plasmapheresis (640.65(b)(8))
- 48 hour interval between any two donations
- Maximum of 104 times per year

FDA Memorandum: *Volume Limits for Automated Collection of Source Plasma*
(4 November 1992)

Donor Weight	Plasma Volume or Weight		Collection Volume	
110-149 lbs	625 mL	(640 g)	690 mL	(705 g)
150-174 lbs	750 mL	(770 g)	825 mL	(845 g)
≥ 175 lbs	800 mL	(820 g)	880 mL	(900 g)

Donation Volumes

United States Compared to Europe

United States	Germany	Council of Europe
Twice/week 104 times/year 63-83 L/year	Once/week 45 times /year 29-38 L/year	Once/week 45 times /year 25 L/year
110-149 lbs 625 mLs	Up to 60 Kg (132 Lbs) 650 mLs	Up to 60 Kg (132 Lbs) 650 mLs
150-174 lbs 750 mLs	60 - 80 kg (132-176 lbs) 750 mLs	60 - 80 kg (132-176 lbs) 650 mLs
175 lbs and up 800 mLs	80 kg and up, (176 lbs +) 850 mLs	80 kg and up, (176 lbs) 650 mLs

CBER Donor Fatality Reporting

21 CFR 640.73 Subpart G – Source Plasma

“If a donor has a fatal reaction which, in any way, may be associated with plasmapheresis...”

- Immediate notification to CBER
- FDA can be reached 24 hours/day, 7 days/week
- Written follow-up report within 7 days

CBER Fatality Review Committee

- Consists of a team of CBER medical officers and an expert from the Office of Compliance
- Reviews every donation and transfusion related fatality report
- Makes a determination on donation as a potential cause of death

Source Plasma Donor Fatality Investigation

- Donor records for previous 2 years
- Hospital records for the donor (including autopsy) if applicable and available
- Plasmapheresis device performance logs, maintenance records, manufacturer notices, part recalls for past 2 years

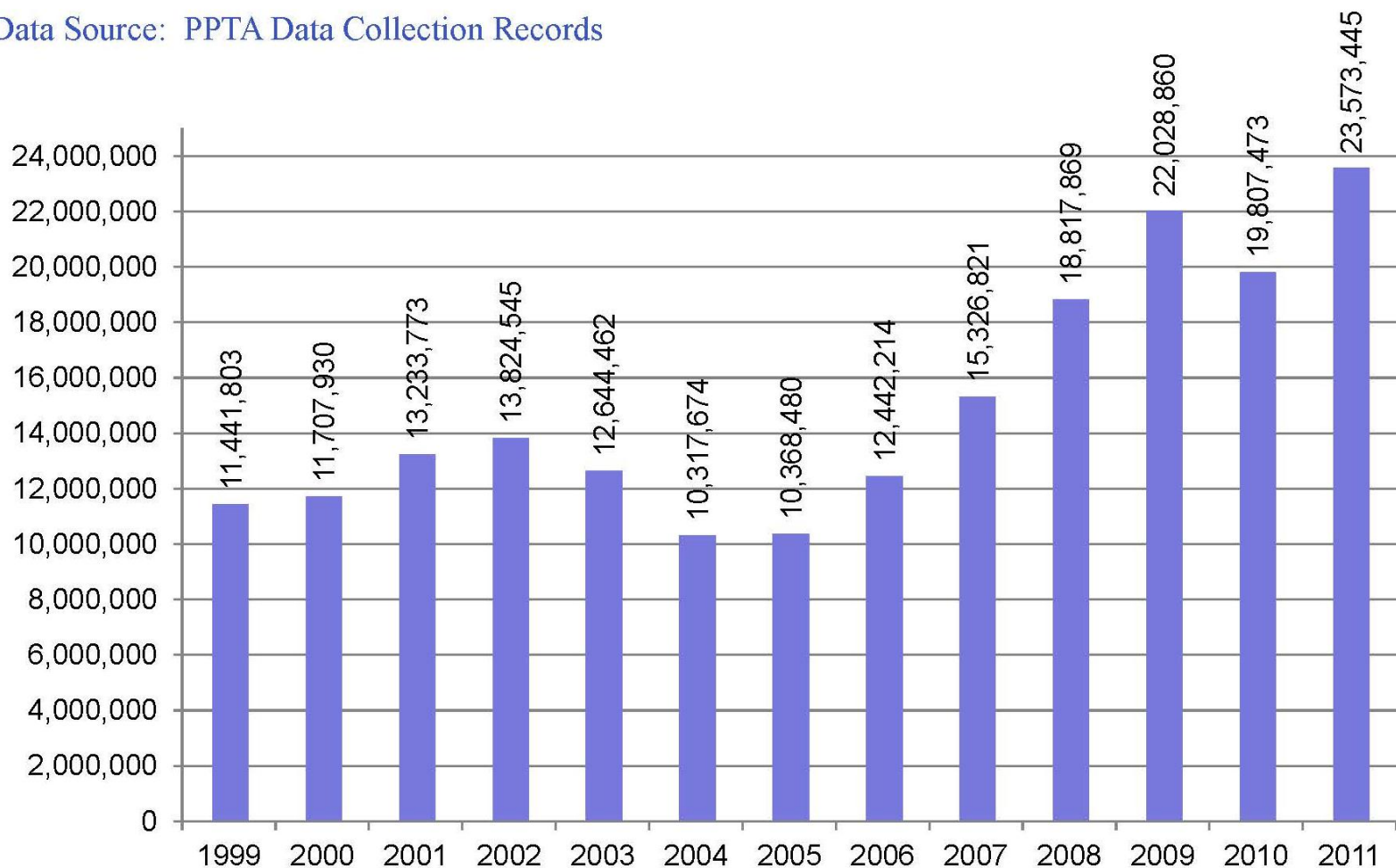
Fatality Decision Table

Fatality related to the donation	Donation confirmed as the cause of death
Fatality not related to the donation	Donation ruled out as the cause of death i.e., homicide, drug overdose
Fatality not ruled out	Donation not ruled out as the cause of death

Post-Donation Fatality Reports by Donated Product, FY2007 - FY2011

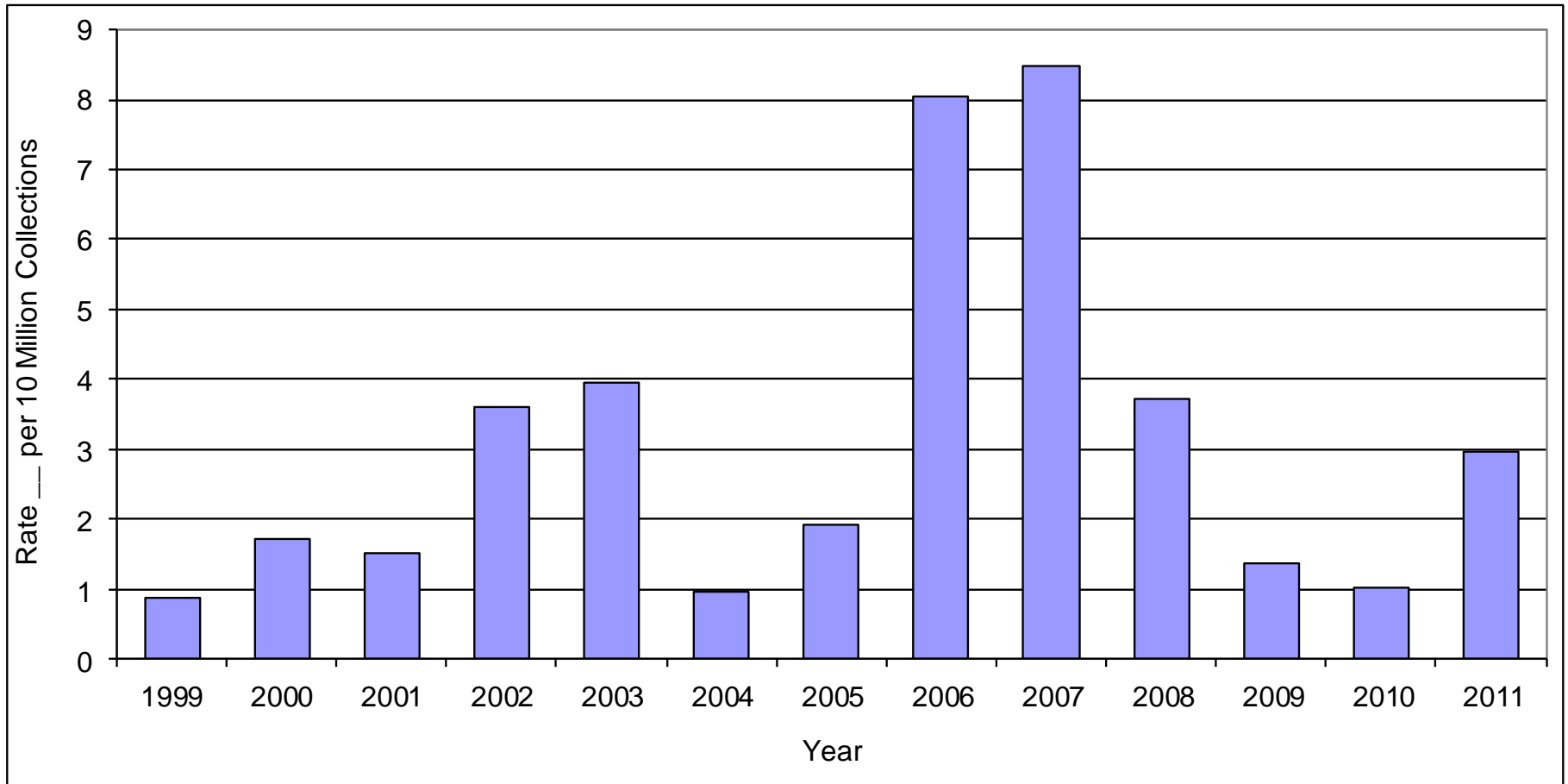
Donated Product	FY07	FY08	FY09	FY10	FY11
Source Plasma	13	7	3	2	7
Whole Blood	2	2	3	3	2
Apheresis Platelets	2	0	0	0	0
Apheresis Red Blood Cells	0	1	0	0	1
Total	17	10	6	5	10

Data Source: PPTA Data Collection Records

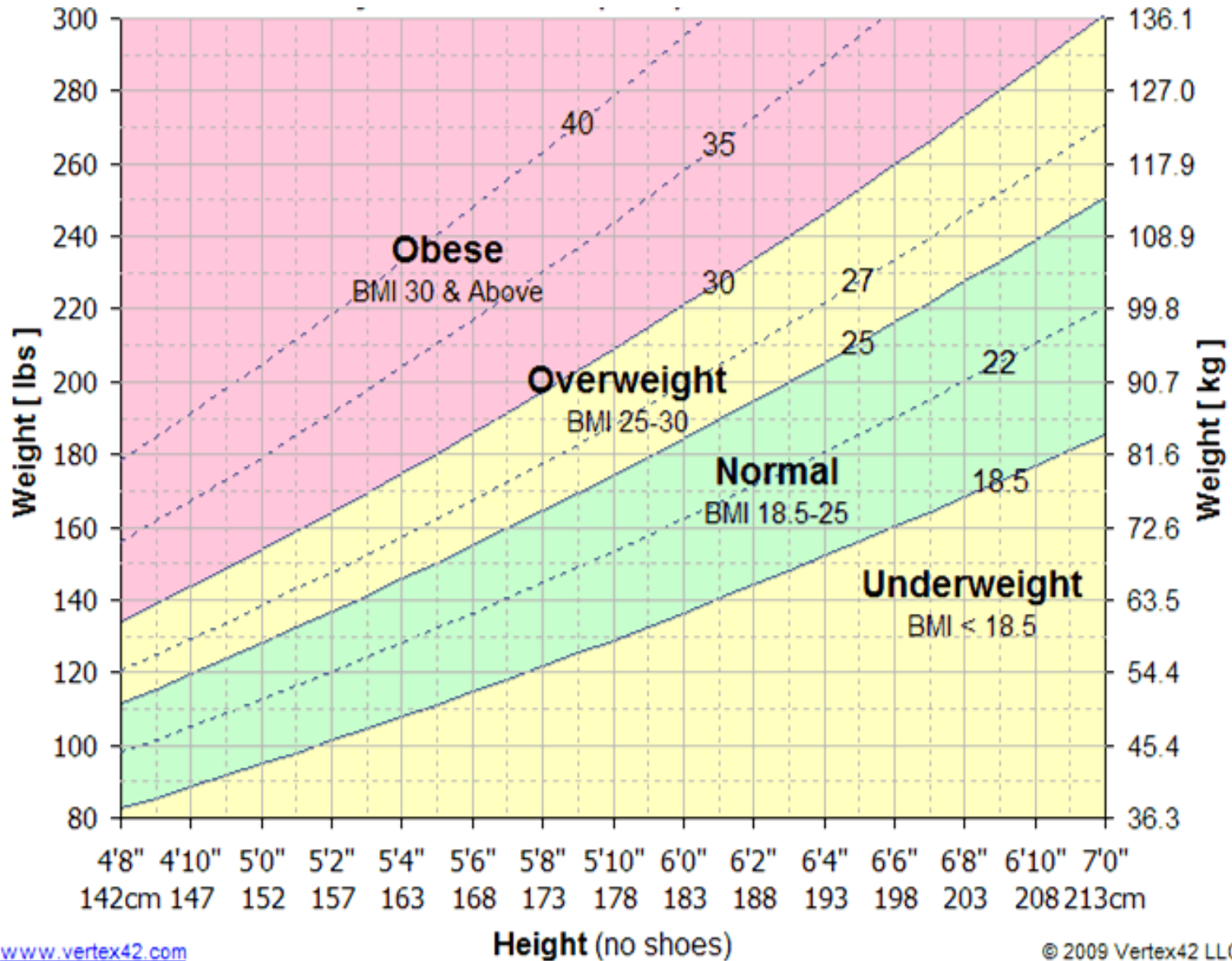


Rate of Source Plasma Donor Fatality Reporting 1999 - 2011

(# of Fatalities Reported to FDA per 10 Million Collections)



Body Mass Index (BMI) for Adults



Effect of Weight on Blood Volume

- Circulatory system is a closed system sensitive to changes in blood volume
- Blood volume is 79 mL/kg \pm 10% for both lean males and lean females
- As body weight increases, total blood volume does not increase proportionally. The blood volume to body weight may fall toward approximately 43-45 mL/kg

Feldshuch L, Enson Y Prediction of Normal Blood volume Relation of blood volume to body habitus *Circulation* 1977; 56:605-612

Plasma loss and blood volume

Loss of plasma can be medically significant:

- Plasma loss can raise the heart rate and can cause a symptomatic drop in blood pressure.
- Plasma loss can result in hemoconcentration with resultant hyperviscosity and a hypercoagulable state.
- A severe loss can cause hypovolemic shock similar to that caused by hemorrhage.

Summary of Observations

2005 – 2011 data

1. When corrected for changes in collection numbers, annualized rates for reported fatalities following Source Plasma Donation range from 1.0 to 8.5 per ten million.
2. The three year moving average, has been relatively stable at 2-7 reported fatalities per ten million donations.
3. There does not appear to be a stable up or down trend in rates over time.
4. A spike in reporting in 2006-2007 was attributed to a change in case ascertainment by a major collector.

Analytic Parameters for Consideration (I)

- Temporal association with donation (clustering) vs random deaths
- Trends in annual fatality data vs random events
- Variations in reporting
 - Definitions
 - Observation period following donation
 - Proactive investigation vs passive reporting

Analytic Parameters for Consideration (II)

- Demographics of cases compared to background donors
 - Age
 - Gender
 - Race
 - Socioeconomic status/Education

Analytic Parameters for Consideration (III)

- Medical condition of cases compared to background among donors and the general population
 - Weight
 - BMI (derived from height and weight)
 - Underlying medical history (determined)
 - Underlying medical history (undetermined)
 - Physical condition
 - Donation History

Analytic Parameters for Consideration (IV)

- Day of donation factors
 - Hydration
 - Medication (e.g. diuretics)
 - Lack of medication (e.g. anti-hypertensives)
 - (Stress)

Other Analytic Approaches

- Need for standardized investigation and reporting of adverse events associated with donation
- Surveillance power will be increased by future required reporting of non-fatal Severe Adverse Events (SAEs) potentially caused by donation (e.g. cardiac).

FDA Considerations for Donor Safety

- FDA (and industry) will take immediate action if current donation procedures are found to be of concern for donor health
- Potential Future Interventions could include:
 - Adjustment of plasma volume nomogram (BMI)
 - Modification of inter-donation interval
 - Combination of both
 - Mitigations related to apheresis devices
 - Additional donor safety considerations based on any recognized co-factors