

HCT/P Compliance Update

5th Annual FDA and the Changing
Paradigm for HCT/P Regulation

Las Vegas, NV, January 28, 2009

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U.S. Department of Health and Human Services
Food and Drug Administration

Summary

- Inspections by the numbers
- Inspectional Observations
- Regulatory citations
- HCT/P cases
- HCT/P Deviation Reports
- Recalls

Inspections



FY08 HCT/P Inspections Accomplished

Type of HCT/P establishment	# Inspections Accomplished	Hours/Inspection
Reproductive tissues	158	42.4
Cord blood stem cells	19	31.7
Peripheral blood stem cells		
All other HCT/Ps (e.g. musculoskeletal, ocular, recovery, distributors)	213	34.4
Total	383*	37.5

*Sum of individual inspections do not equal total due to some inspections that were conducted for products in multiple categories

FY08 HCT/P Inspection Classifications

Type of HCT/P establishment	NAI	VAI	OAI
Reproductive tissues	106	40	10
Cord blood stem cells	15	4	0
Peripheral blood stem cells			
All other HCT/Ps (e.g. musculoskeletal, ocular, recovery, distributors)	164	46	1
Total	285	90	11

FDA Form 483

- “This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above....”

OAI/VAI/NAI?

- OAI – Official Action Indicated –
objectionable conditions found that warrant action
- VAI – Voluntary Action Indicated –
objectionable conditions found but do not meet the threshold for regulatory action
- NAI – No Action Indicated – no
objectionable conditions found (generally no FDA-483)
- http://www.fda.gov/ora/inspect_ref/fmd/fmd86.htm

FY08 HCT/P Inspection Results

- Approx. 30% of HCT/P inspections resulted in issuance of Form FDA-483s;
- Consistent with FY07 and FY06.

Inspectional Observations: Storage and Distribution

- Failure to store HCT/Ps at appropriate temperatures; establish acceptable temperature limits; and/or maintain and record storage temperatures 21 CFR 1271.260 (b) and (e)
 - Storage room temperatures are not recorded
 - Freezer did not have a functioning recording device and was not equipped with an alarm. The freezer temperature is not recorded or monitored after normal operating hours
 - Temperature monitoring logs not reviewed prior to removal/transfer of grafts as required in the SOP

Inspectional Observations: Processors

- Failure to maintain facility in good state of repair 21 CFR 1271.190(a)
 - Several processing rooms have damage to the walls – areas of damage show exposed dry wall below the level of the paper layer
- Failure to maintain documentation of equipment maintenance, cleaning, sanitization and calibration 21 CFR 1271. 200(e)
 - Cleaning of equipment was not documented. There were no records of cleaning from 1/2006 – 3/2008

Inspectional Observations: Processors - 2

- Failure to process HCT/Ps in a way that does not increase the risk of introduction, transmission or spread of communicable disease 21 CFR 1271.220(a)
 - There were five occurrences where containers holding tissue from two different donors were opened at the same time in the processing hood. (Note – a cross contamination event had been documented)

Inspectional Observations: Donor Testing

- Failure to perform testing for communicable disease agents according to the manufacturer's instructions 21 CFR 1271.80(c)
 - Cadaveric samples tested by NAT assay were routinely tested using a 1:5 dilution. The package insert instructs that cadaveric donors be tested "neat."

Regulatory Actions



Regulatory Actions

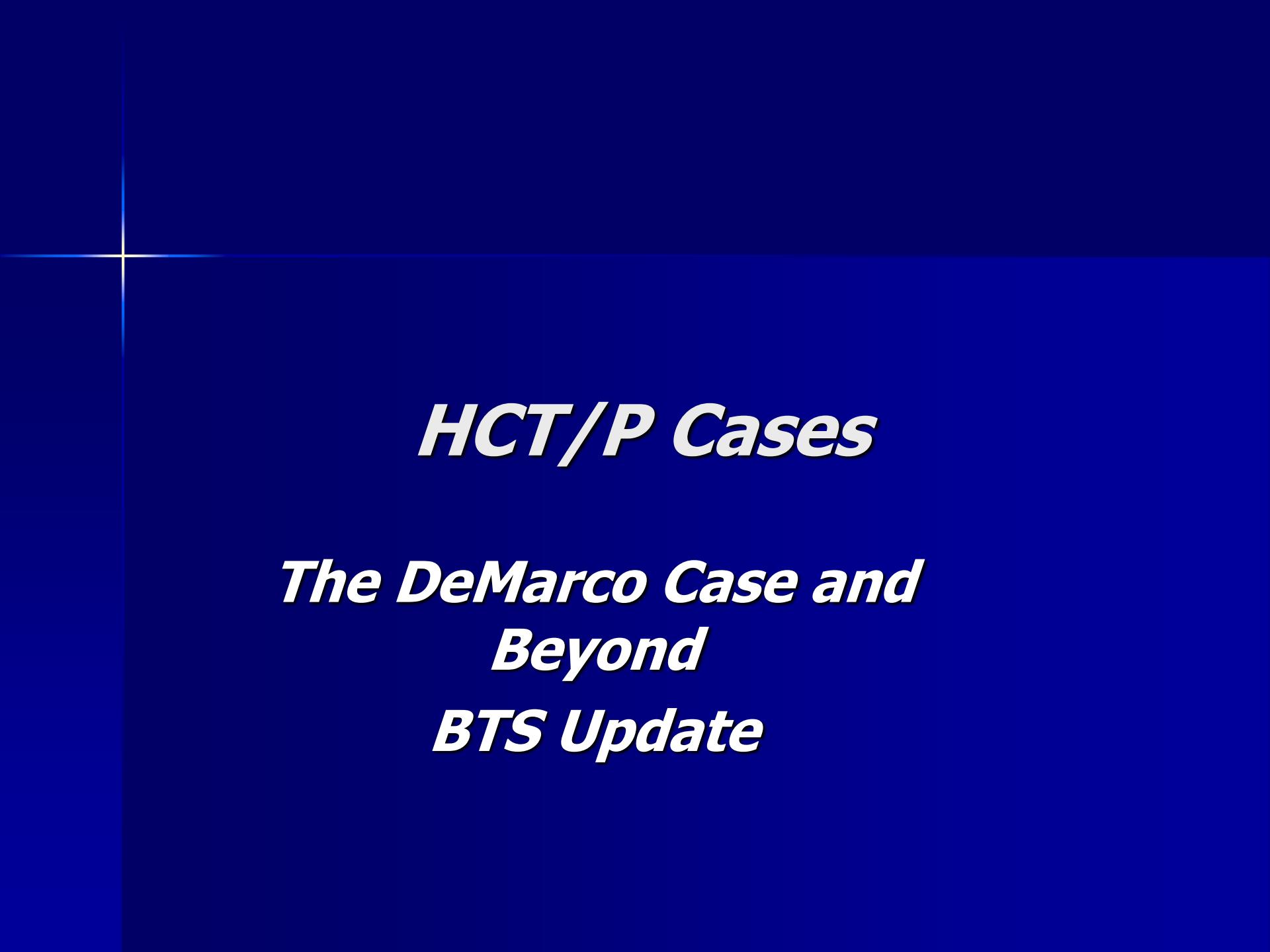
- Regulatory Actions Issued
 - 1 Warning Letter (repro)
 - 1 Untitled Letter (repro)
 - 1 Untitled Letter –website/stem cell treatment – part of our internet surveillance

FY08 HCT/P Regulatory Actions: Deviations Cited

- Failure to test specimens from anonymous or directed reproductive donors using appropriate **FDA-licensed, approved, or cleared donor screening tests**, in accordance with the manufacturer's instructions 21 CFR 1271.80(c).
- Failure to screen an anonymous or directed reproductive donor of cells or tissue by reviewing the donor's relevant medical records for risk factors for, and clinical evidence of, relevant communicable disease agents and diseases 21 CFR 1271.75(a).

Regulatory Actions - 2

- Failure to establish and maintain procedures for all steps that are performed in testing, screening, determining donor eligibility, and complying with all other requirements of Subpart C "Donor Eligibility" in 21 CFR Part 1271. "Establish and maintain" means define, document, and implement; then follow, review, and as needed, revise on an ongoing basis [21 CFR 1271.47(a)].
 - The firm's standard operating procedures did not address all steps required for donor screening and determining donor eligibility, including, but not limited to: (1) donor screening for risk factors for, or clinical evidence of relevant communicable disease agents and diseases; and (2) the criteria used to determine donor eligibility and ineligibility.



HCT/P Cases

*The DeMarco Case and
Beyond
BTS Update*

DeMarco*

- In September 2006, Charlene DeMarco, a former doctor of osteopathy and her co-conspirator Elizabeth Lerner, a.k.a. “Elizabeth Cooperman,” were convicted of all charges contained in an 11-count federal indictment: one count of conspiracy to commit mail and wire fraud, three counts of mail fraud, six counts of wire fraud and one count of money laundering.

*From FDA News Release , December 19, 2007

DeMarco (cont...)

- “Evidence showed that from October 2002 until November 2004, DeMarco and Lerner agreed to defraud amyotrophic lateral sclerosis (ALS)* patients and their families by claiming they could treat ALS patients with stem cell therapy, when they knew they could not. The defendants falsely told the patients and their families that DeMarco had previously received FDA approval to treat ALS.”

*commonly called Lou Gehrig’s disease

DeMarco (cont...)

- In September 2007, Charlene DeMarco, was sentenced to 57 months in prison, ordered to pay \$32,190 in restitution to victims and a criminal fine of \$7500.
- In December 2007, Elizabeth Lerner was sentenced to 33 months in prison, ordered to pay \$35,390 in restitution to victims and a criminal fine of \$7500.



The Other Side of the Coin

- **The National Marrow Donor Program**
 - **Public program, relies on unrelated allogeneic donors**
 - **Hematopoietic stem cells obtained from peripheral blood or cord blood are available to any patient**
 - **Registry of potential peripheral blood stem cell donors**
 - **Registry of cord blood units**
 - **Searchable to match donor or unit to recipient for hematopoietic reconstitution in patients with hematological malignancies**
 - **“Draft Guidance for Industry: Minimally Manipulated, Unrelated, Allogeneic Placental/Umbilical Cord Blood Intended for Hematopoietic Reconstitution in Patients with Hematological Malignancies,” issued 1/16/07**

Private Banking: Wave of Future?

- Autologous – you pay to bank for future, possible need
 - Cord blood – potential use for siblings too; also baby teeth
 - Adult stem cells – different sources advertised



Questioning the Allure of Putting Cells in the Bank

By ANDREW POLLACK

Published: January 29, 2008

FDA Regulations

- Establishments that collect, process and store (the bank) and potentially distribute, are manufacturing HCT/Ps and, as the use is autologous and/or 1st and 2nd degree family related allogeneic, are regulated under section 361 of the Public Health Service Act and 21 CFR part 1271.

Concern

- Maintenance of proper conditions during long-term storage
- Banks promote that these HCT/Ps will cure or mitigate diseases (e.g. Parkinson's Disease), and these claims are unproven
- The manufacturer's objective intent is one of the factors taken into account in determining the level of regulation of HCT/Ps
- Such promotion might result in a determination that the HCT/P be regulated as a biological product under section 351 of the PHSA
- A biological product must be distributed under an FDA-monitored IND, or the manufacturer must prove to FDA that the product is safe and effective, and be licensed

Biomedical Tissue Services (BTS) Order to Cease and Retain HCT/Ps

- Immediately cease manufacturing operations and retain HCT/Ps.
- To BTS and its CEO and Executive Director, Michael Mastromarino, D.D.S.
- After initially focusing efforts on assessing the safety of distributed tissue and facilitating recalls, FDA determined that the violations uncovered at BTS, because of their serious nature, constitute a danger to health and took this unprecedented action
- Order to Cease Manufacturing and to Retain HCT/Ps issued January 31, 2006
- **www.fda.gov/cber/compl/bts013106.htm**

BTS Order

- Despite records maintaining otherwise:
 - The firm inadequately screened donors for risk factors for, or clinical evidence of, relevant communicable disease agents and diseases;
 - FDA found numerous instances where death certificates maintained in BTS' files were at variance with the death certificates FDA obtained from the state where the death occurred:
 - Cause, place, and time of death, and the identity of next of kin.
- FDA continued to work with other federal, state and local authorities

CDC: MMWR

Brief Report May 26, 2006

- "Investigation into Recalled Human Tissue for Transplantation---United States, 2005--2006."
- Approximately 25,000 BTS-recovered tissue products distributed to all 50 states and internationally
- FDA and CDC continue to investigate reports of BTS recipients who have undergone screening and tested positive for one of the four tested diseases
- Some positive results would be expected in any U.S. population tested (prevalence data provided)

MMWR cont..

- Relationship between implanted BTS tissue and positive test results reported to FDA and CDC is difficult to ascertain because of inaccurate BTS donor records and, in some cases, the absence of properly linked donor samples.

BTS Update

- In March 2008, Michael Mastromarino pleaded guilty in Brooklyn Supreme Court to body stealing, forgery, grand larceny and enterprise corruption and was sentenced to 18 to 54 years. He is serving a concurrent sentence of 25 to 58 years after pleading guilty to similar charges in Philadelphia.
- Co-defendant Lee Cruceta pleaded guilty to conspiracy, taking part in a corrupt organization, abuse of a corpse and 244 counts each of theft and forgery in Philadelphia and also has pleaded guilty to related charges in Brooklyn and negotiated pleas to serve concurrent sentences of 6½ to 20 years.
- Co-defendant Chris Aldorasi was found guilty of enterprise corruption and other criminal counts in Brooklyn and sentenced to 9 to 27 years.

BTS Update - 2

- Co-defendant Joseph Nicelli has yet to stand trial in Brooklyn
- On December 12, 2008, Jason Gano, a former funeral director in Rochester, NY, was found guilty of 17 counts each of opening graves, body stealing, and unlawful dissection, as well as one count of scheming to defraud. He faces up to 20 years in prison when he is sentenced.
- Six others are expected to stand trial in Rochester
- FDA will continue to work cooperatively with other Federal, State and local authorities

HCT/P Deviation Reporting

	FY06	FY07	FY08
Reportable	144	153	223
<i>Electronic Reports</i>	100 (69%)	118 (77%)	164 (74%)
Non-Reportable	76	48	63
Total Reports	220	201	286

HCT/P Deviation Reports

Products Involved

Product	FY06	FY07	FY08
Peripheral Blood Stem Cells	71	98	109
Cornea/Sclera	51	35	44
Skin	6	6	27
Musculoskeletal	21	14	26
Somatic Cells	0	1	19
Donor Leukocytes	6	10	12
Cord Blood Stem Cells	2	4	4

HCT/P Deviations Reported

Reportable HCT/P Deviations	FY 05	FY 06	FY 07	FY 08
Donor Eligibility	8	32	24	37
Donor Screening	0	12	8	17
Donor Testing	0	33	54	54
Environmental Control	0	1	2	0
Supplies and Reagents	0	3	6	1
Recovery	0	2	8	8
Processing	0	14	17	68
Labeling Control	1	2	1	2
Storage	0	1	0	0
Receipt, Pre-Dist., Dist.	4	43	32	36
Total	13	143	152	223
Non-Reportable	15	77	48	63

HCT/P Deviation Reports

Non-Reportable Events

- No products were distributed
- Not associated with disease transmission or contamination
- Not related to core GTP
- Product released under urgent medical need
- Product not subject to HCT/P deviation reporting
 - Reproductive tissue
 - Unrelated Allogeneic Stem Cells
- Reporting establishment is not an HCT/P manufacturer

HCT/P Deviation Reports

Non-Reportable Events

- Positive pre-implant culture is in general not reportable as a deviation
 - Unless a complaint results in an investigation that reveals a departure from GTPs or
 - If the recipient had an adverse reaction then might be reported as an adverse reaction not HCT/P deviation

HCT/P Deviation Reporting FY08

HCT/P Deviation Code	Cellular HCT/P	Tissue HCT/P	Total	
Donor Eligibility	4	33	37	<u>16.6%</u>
Donor Screening	2	15	17	7.6%
Donor Testing	42	12	54	<u>24.2%</u>
Environmental Control	0	0	0	0.0%
Supplies and Reagents	1	0	1	0.4%
Recovery	8	0	8	3.6%
Processing and Processing Controls	50	18	68	<u>30.5%</u>
Labeling Controls	0	2	2	0.9%
Storage	0	0	0	0.0%
Receipt, Pre-Distribution, Shipment & Distribution	33	3	36	<u>16.1%</u>
Total	140	83	223	100%

Tissue HCT/P Reports

- Donor Eligibility – 33 reports
 - Donor accepted when risk factors, clinical evidence or physical evidence identified – 18
 - Donor accepted when reactive for relevant communicable disease – 4
 - Donor incorrectly evaluated for plasma dilution – 10
 - Donor testing not performed or documented - 1

Tissue HCT/P Reports - 2

- Processing and process controls – 18
 - HCT/P contaminated, potentially contaminated or cross contaminated – 17
 - In-process controls inadequate – 1

- Microorganisms involved:
 - *Bacillus, Candida, Clostridium, Enterobacter, Group D Enterococcus, Staphylococcus, Proteus*

Tissue HCT/P Reports - 3

- Donor Screening – 15
 - Donor screening not performed or documented – 1
 - Donor screening (medical history interview) performed incorrectly (incomplete or inaccurate) – 13
 - Donor screening (medical record review) performed incorrectly (incomplete or inaccurate) - 1

Cellular HCT/P Reports

- Donor testing – 42
 - Inappropriate test or test lab used; Required test not FDA licensed, approved or cleared – 41
 - Six of the above represent HIV/HCV NAT performed on pooled instead of individual samples
 - Specimen tested was collected from a PBSC donor more than 30 days before recovery - 1

Cellular HCT/P Reports - 2

- Processing and process controls – 50
 - HCT/P contaminated, potentially contaminated or cross contaminated during processing – 47
 - One event related to syringe integrity
 - In process controls not followed – 3
- Microorganisms involved:
 - *Diphtheroids, Enterobacter, Group D Enterococcus, Klebsiella, Micrococcus, Peptostreptococcus, Propionibacterium, Staphylococcus, Stenotrophomonas, Streptococcus*

Cellular HCT/P Reports - 3

- Distribution – 33
 - Contaminated or potentially contaminated HCT/P – 32
 - Distribution without sign off by a responsible person – 1

- Microorganisms involved:
 - *Bacillus, Cladosporium, Corynebacterium, Lactobacillus, Penicillium, Propionibacterium, Staphylococcus*

Classified Recalls

FY 2007

	HCT/P Recalls	CBER Total Recalls (all products)
FY 07 Class I	7	7
FY 07 Class II	15	1041
FY 07 Class III	0	381

Classified Recalls

*FY 2008**

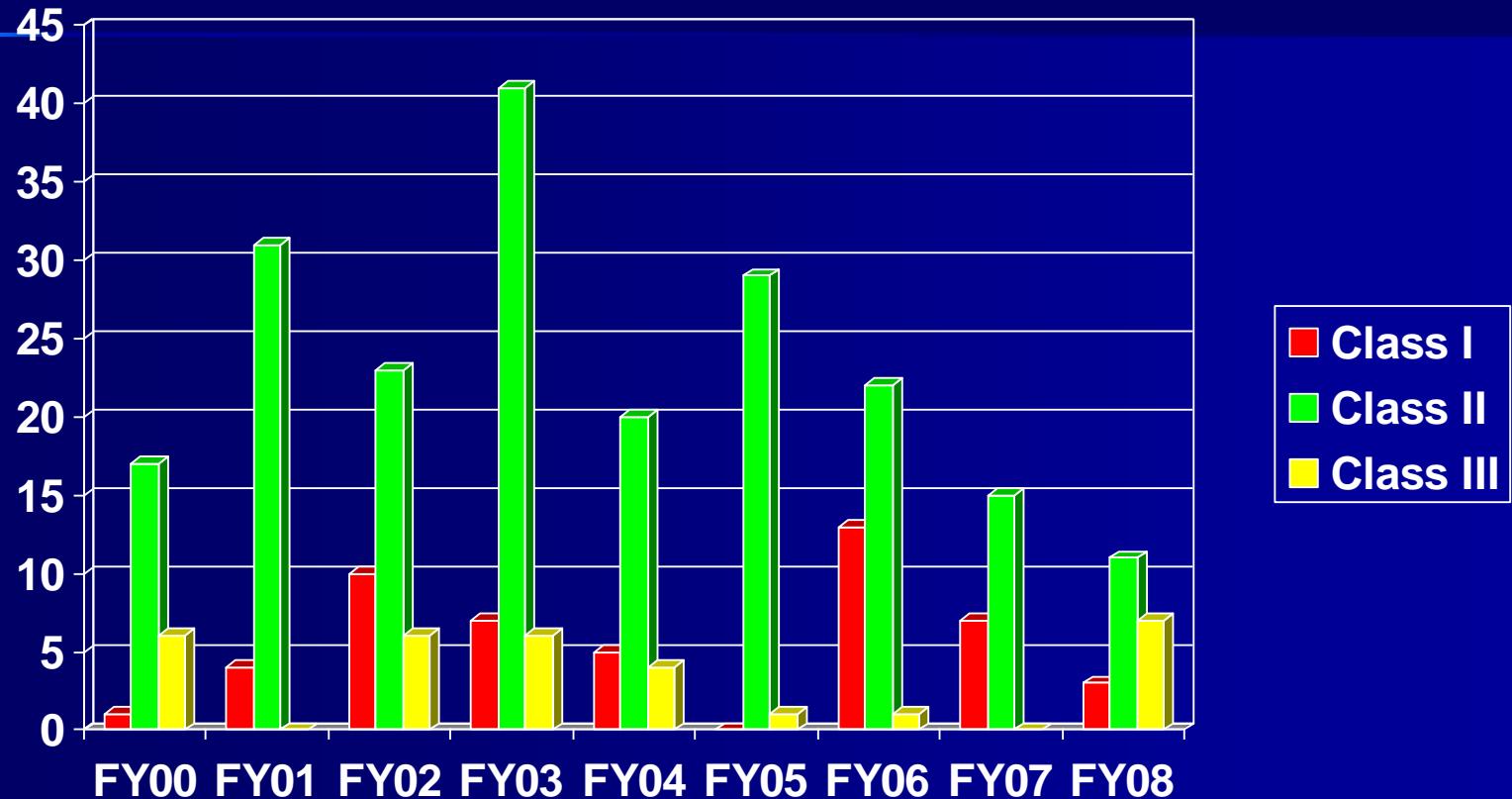
	HCT/P Recalls	CBER Total Recalls (all products)
FY 08 Class I	3	4
FY 08 Class II	11	950
FY 08 Class III	7	345

*- This table does not include 3 "mixed class" recalls

FY 2008 Class I HCT/P Recalls

- Donors met all DE requirements using diagnostic HBsAg and HBcAb tests. Re-testing of donors using FDA licensed donor screening tests revealed three donors reactive (confirmed positive) for HBsAg
 - 2 recalls
- *Clostridium perfringens* infection in recipient.

HCT/P Recalls



Vision for CBER

***INNOVATIVE TECHNOLOGY
ADVANCING PUBLIC HEALTH***

CBER uses sound science and regulatory expertise to:

- Protect and improve public and individual health in the US and, where feasible, globally**
- Facilitate development, approval and access to safe and effective products and promising new technologies**
- Strengthen CBER as a preeminent regulatory organization for biologics**

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