CBER Update

13th Annual GMP by the Sea

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Mary Malarkey, Director

Office of Compliance and Biologics Quality

FDA

U.S. Department of Health and Human Services

Food and Drug Administration

Summary

- Selected rules and guidance
- The Numbers
  - Biological Product Deviation Reports
  - Recalls
  - Advisory Actions
- Cases

Rules and Guidance

- Live Virus Processing – 21 CFR 600.11(e)(4) – effective date 3/18/08
  - Old rule required separate areas and equipment for production of live viruses (vaccines) up until filling
  - New rule allows greater flexibility for manufacturers regarding the buildings and equipment used for live virus processing at all stages of manufacture.
- Same principles as Spore Former Rule

Rules and Guidance (cont..)

- “Guidance for Industry: Manufacturing Biological Intermediates and Biological Drug Substances Using Spore-Forming Microorganisms,” issued 9/6/07
- “Guidance for Industry: Considerations for Plasmid DNA Vaccines for Infectious Disease Indications,” issued 10/29/07
- “Guidance for Industry Providing Regulatory Submissions to the Center for Biologics Evaluation and Research (CBER) in Electronic Format - Lot Release Protocols,” issued 11/27/07

Rules and Guidance (cont…)

- “Draft Guidance for Industry: Validation of Growth-Based Rapid Microbiological Methods for Sterility Testing of Cellular and Gene Therapy Products,” issued 2/11/08
- “Guidance for Industry: Container and Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products,” issued 2/22/08

Rules and Guidance (cont…)

- “Draft Guidance for Industry: Considerations for Allogeneic Pancreatic Islet Cell Products,” issued 5/21/08
- “Draft Guidance for Industry: Nucleic Acid Testing (NAT) to Reduce the Possible Risk of Parvovirus B19 Transmission by Plasma-Derived Products,” issued 7/30/08

Rules and Guidance (cont…)

- Amendment to the Current Good Manufacturing Practice Regulations for Finished Pharmaceuticals; Direct Final Rule and Companion Proposed Rule, published 12/4/07
- Withdrawal of 1996 amendments 12/4/07
- Amendment to the Current Good Manufacturing Practice Regulations for Finished Pharmaceuticals; Withdrawal, published 4/4/08
  - "The agency received significant adverse comments. FDA will consider the comments received under our usual procedures for notice and comment in connection with the notice of proposed rulemaking"

GMP Regulations Working Group

- The Amendments represent the first phase of the incremental approach to modifications of parts 210 and 211 under the agency's Pharmaceutical CGMP for the 21st Century initiative
- The GMP Regulations Working Group is addressing comments to finalize the proposed rule.

Rules and Guidance (cont..)

- Current Good Manufacturing Practice and Investigational New Drugs Intended for Use in Clinical Trials – effective date 9/15/08
  - Exempts most phase 1 investigational drugs from complying with the regulatory CGMP requirements.
  - FDA will continue to exercise oversight of the manufacture of these drugs under FDA's general statutory CGMP authority and through review of the investigational new drug applications (IND).
- "Guidance for Industry: CGMP for Phase 1 Investigational Drugs," issued 7/15/08

The Numbers

FY04-07 – Classified Recalls

Product	FY04	FY05	FY06	FY08
Blood	1773	2130	1633	1240
Source Plasma	242	263	150	132
Derivative	2	3	0	0
IVD	3	8	4	1
Vaccine	2	0	1	3
Therapeutic	0	0	0	0
Allergenic	1	0	0	0
Device	6	16	17	17
Tissue	29	30	36	22
TOTAL	**2058**	**2450**	**1841**	**1415**

FY07 - Biological Product Deviation Reports – Drugs and Devices

	FY05		FY06		FY07		%
Firm	#BPD	#eBPD	#BPD	#eBPD	#BPD	#eBPD	
Allergenic	200	187	149	132	174	151	86.8
Plasma Derivative	47	14	35	18	59	33	55.9
Device	100	53	60	41	69	42	60.9
Vaccine	39	2	41	4	60	7	**11.7**
Total	**387**	**256**	**286**	**195**	**363**	**233**	
		66.5%		68.2%		64.2%	

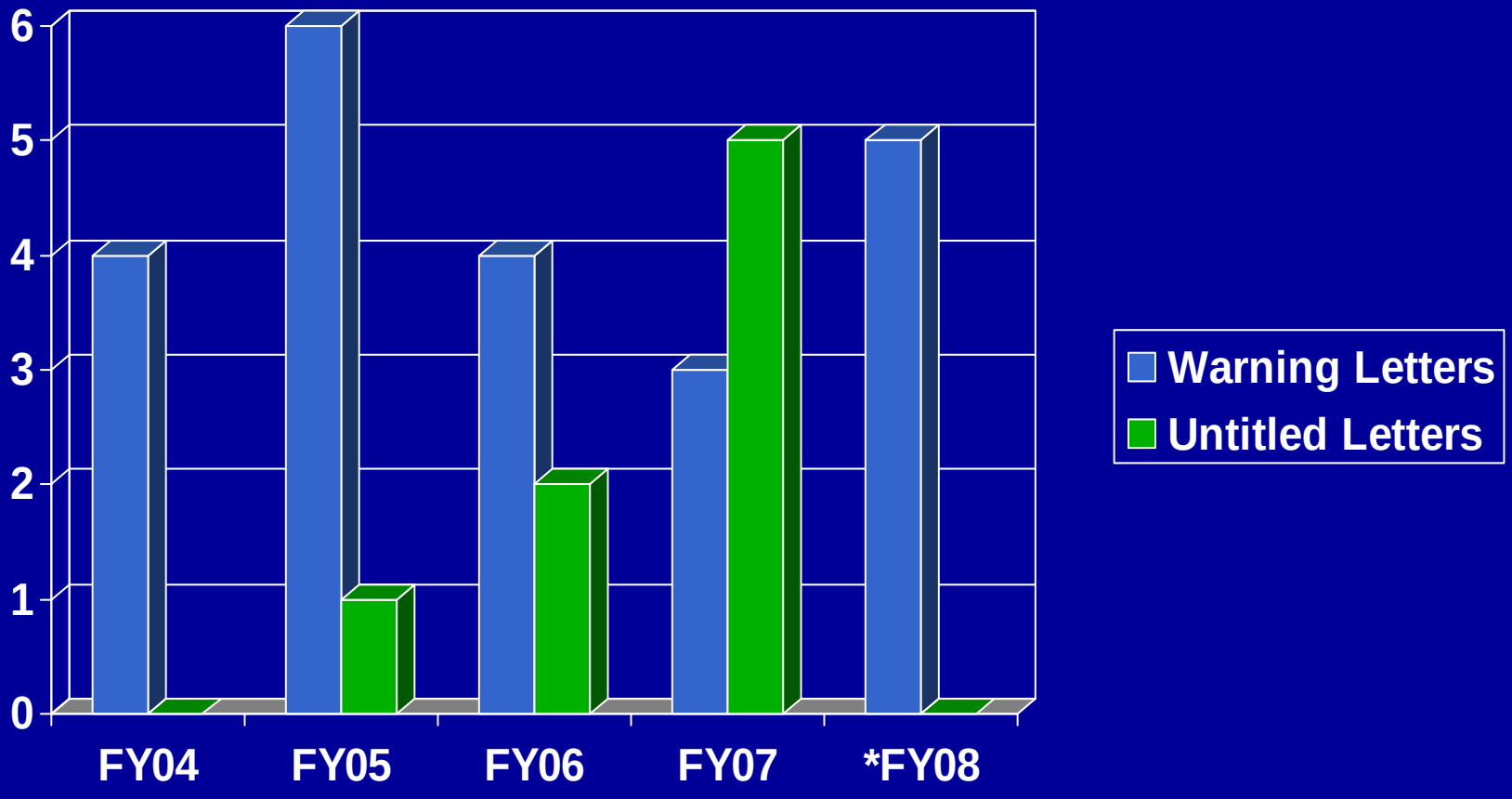
BPDR FY07 Notes

- 26% overall increase compared to FY06
- Allergenic manufacturers submitted the highest number, 86.8% of reports electronically
- Vaccine manufacturers submitted the lowest number, 11% of reports electronically
- To put in perspective, 94.3 % of licensed blood establishment reports are now submitted electronically
- This provides for more effective and efficient processing and use of information

FY07- Biological Product Deviation Reports – Drugs and Devices

MANUFACTURING SYSTEMS			
	FY05	FY06	FY07
Incoming Material Specifications	15	5	6
Process Controls	28	26	42
Testing	21	18	32
Labeling	73	33	30
Product Specifications	235	181	231
QC & Distribution	13	22	20
Miscellaneous	0	1	2

Biological Drug and Device



*As of July 31, 2008

Top Five Citations – Biological Drugs

Citation	Citation Language
211.192	"You failed to thoroughly investigate any unexplained discrepancy or the failure of a batch or any of its components to meet any of its specifications, as follows…"
211.22	"The deficiencies described in this letter are indicative of your quality control unit not fulfilling its responsibility to assure the identity, strength, quality, and purity of your drug product"
211.160	"You failed to establish and follow scientifically sound and appropriate specifications, standards, sampling plans, and test procedures….. and to ensure that such specifications, standards, plans, and procedures, including any changes, are reviewed and approved by the quality control unit"
211.100	"Your firm failed to establish and follow written procedures, and to justify any deviation from written procedures, for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess. "
211.113(b)	"Your firm failed to establish and follow appropriate written procedures designed to prevent microbial contamination of drug products purporting to be sterile and to assure that such procedures include validation of sterilization processes."

Top Five Citations – Biological Drug Intermediates and Substances

- Production and process controls
- Failure Investigations
- Buildings and Facilities
- Equipment Cleaning and Maintenance
- Laboratory Controls
- In addition, general Quality Unit deficiencies often noted

Top Five Citations – Biological Devices

Citation	Citation Language
820.100(a)	"You failed to establish and maintain procedures for implementing corrective and preventive action…"
820.90	"You failed to establish and maintain procedures to control product that does not conform to specified requirements….."
820.198	"You failed to establish and maintain adequate procedures for receiving, review, and evaluation of complaints by a formally designated unit ensuring all complaints are processed in a uniform and timely manner…"
820.70(e)	"You failed to establish and maintain procedures to prevent contamination of equipment or product by substances that could reasonably be expected to have adverse effect on product quality"
820.70(a)	"Failure to establish and maintain process control procedures that describe any process controls necessary to ensure conformance to specifications.."

BIMO –Warning Letters

	FY04	FY05	FY06	FY07
Clinical Investigators	4	12	0	3
Sponsors	0	2	1	1
Sponsor-Investigator	1	0	1	0
IRBs	0	0	3	2
GLP	0	0	0	2

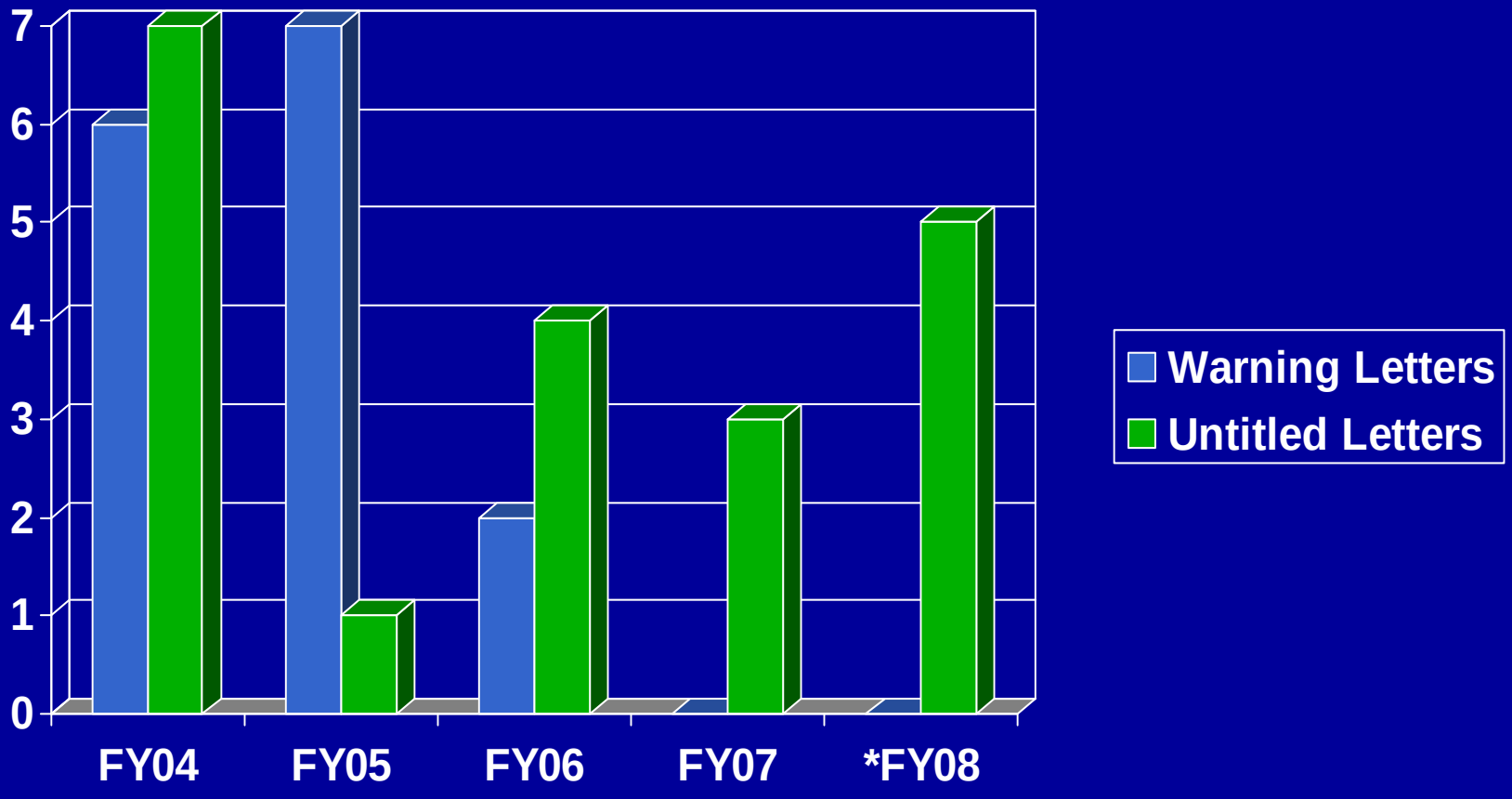
Other BIMO Actions

- FY07
  - One Untitled letter to an IRB
  - One NIDPOE
- FY08 – as of July 31, 2008
  - One Warning letter to a Clinical Investigator
  - One NIDPOE

BIMO

- CBER continues random surveillance to focus on agency priorities and vulnerable populations, e.g. pediatric and elderly
- In FY07, focused also on wound healing products
- Random surveillance has shown substantial compliance with the applicable regulations

Advertising and Promotional Labeling

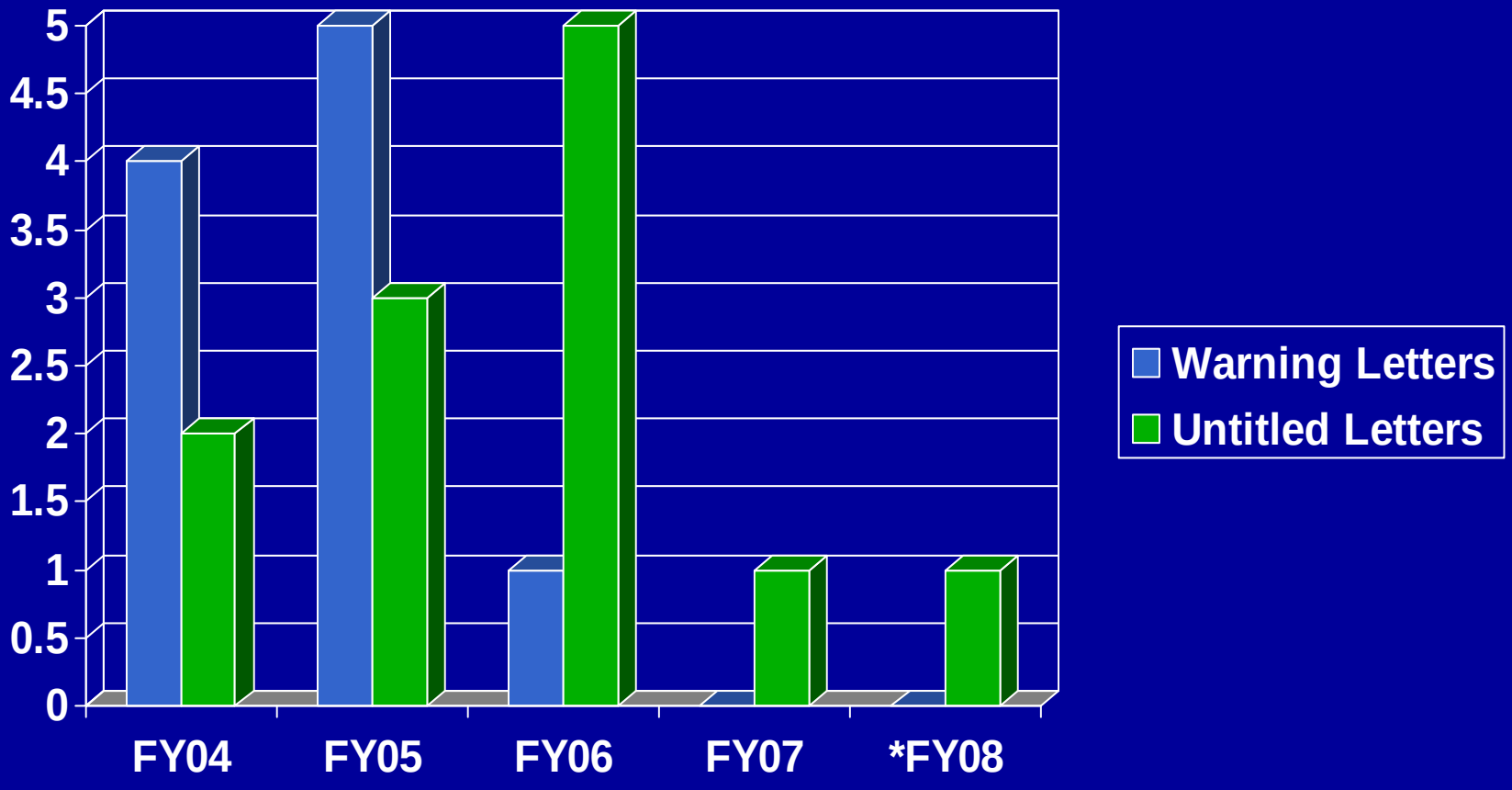


* As of July 31, 2008

FY08 Advertising and Promotion

- Misleading safety and/or efficacy claims
- Superiority claims
- Omission of Material Facts

Internet Surveillance



* As of July 31, 2008

Internet

- Unapproved HIV tests remain a problem
  - On January 29, 2008, FDA posted a Consumer Update, “Vital Facts about HIV Home Test Kits” to further alert consumers

  http://www.fda.gov/consumer/updates/hivtestkit012908.html
- New area of concern – “stem cell” treatments in the U.S.

HCT/P Cases

*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

The New York Times

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, if 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

- The order alleges that FDA's inspection uncovered serious violations of the regulations governing donor screening and record-keeping practices, and:
  - Failure of the firm to follow its own SOPs;
  - Failure to recover HCT/Ps in a manner that does not cause contamination or cross-contamination;
  - Failure to adequately control environmental conditions

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.
- 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.
- Co-defendant Joseph Nicelli has yet to stand trial in Brooklyn
- FDA will continue to work cooperatively with other Federal, State and local authorities

“Success is not final, failure is not fatal: it is the courage to continue that counts”

Winston Churchill

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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- Email CBER:
  - –Manufacturers: matt@cber.fda.gov
  - –Consumers, health care
  - –octma@cber.fda.gov
- Phone:
  - –+1-301-827-1800