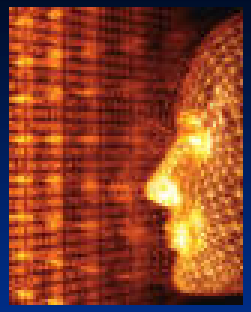
Then and Now: Update on the GTPs for HCT/Ps

2nd Annual FDA and the Changing Paradigm for Tissue Regulation

February 7, 2006

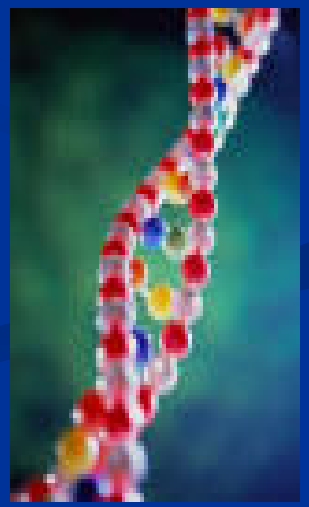
Mary Malarkey, Director, OCBQ, CBER



Vision for CBER

INNOVATIVE TECHNOLOGY ADVANCING PUBLIC HEALTH

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



When we last met…..

- May 25, 2005, was still months away
- Many questions and concerns were expressed and discussed, particularly from the soon to be regulated industries
- There was much work to be done…..

FLASH TO THE FUTURE

Where are we now?

- May 25, 2005, has come and gone
- Training and outreach performed and continuing
- Inspections under Part 1271 have commenced
- Reporting of HCT/P deviations and adverse reactions has commenced
- Policy and guidance development continues

“When it comes to the future, there are three kinds of people: those who let it happen, those who make it happen, and those that wonder what happened.”

John M. Richardson, Jr.,
Professor of International Development,
American University

What has been accomplished since we last met?

Implementation Activities

- Registration of HCT/P establishments
- Training of FDA personnel
- Outreach
- Tissue Policy Team assembled
- Tissue Safety Team (TST) created
- Rule Changes
- Inspection and enforcement
- Recalls
- HCT/P deviation reporting system (Anita Richardson)
- HCT/P adverse reaction reporting system (Su Wang)

HCT/P Registration and Listing
21 CFR 1271.21 to 1271.37

- Registration and listing annually in December
- Form 3356
- Mail, fax or electronic submission
- All the information needed is on the web at http://www.fda.gov/cber/tissue/tisreg.htm
- **New** public query of information in the registration database
  - Query by name, function, status, location
- ~2000 registered establishments

Training of FDA Personnel

- Three courses for experienced investigators completed, with ~150 investigators trained
- Comprehensive training course planned for mid-February 2006
- Review of inspectional findings and feedback

Outreach

- Periodic liaison meetings with professional organizations
  - ISCT
  - AATB
  - AABB
- Participation in the 12th Expert Circle on Human Blood and Tissue – Pharmaceutical Inspections Cooperation Scheme (PIC/S) (inspectors)

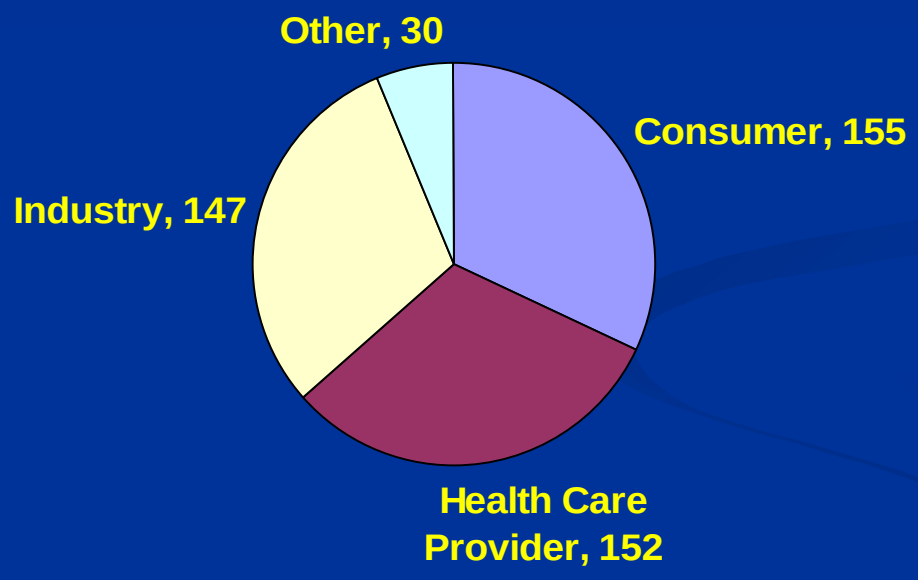
Outreach

- EBAA Quality Workshop – February
- AATB Spring Meeting- March
- ARM FDA Implementation Workshop - March
- ISCT CGTP Workshop- June
- CDC Workshop – June
- AOPO Annual Meeting – June
- APIC Annual Meeting - June
- EBAA Annual Meeting – June
- NATCO Annual Meeting – August
- AAB Reproductive Donor Workshop - September
- ISCT Symposium – September
- AATB Annual Meeting – September
- ASRM Annual Meeting – October
- AAOS - November

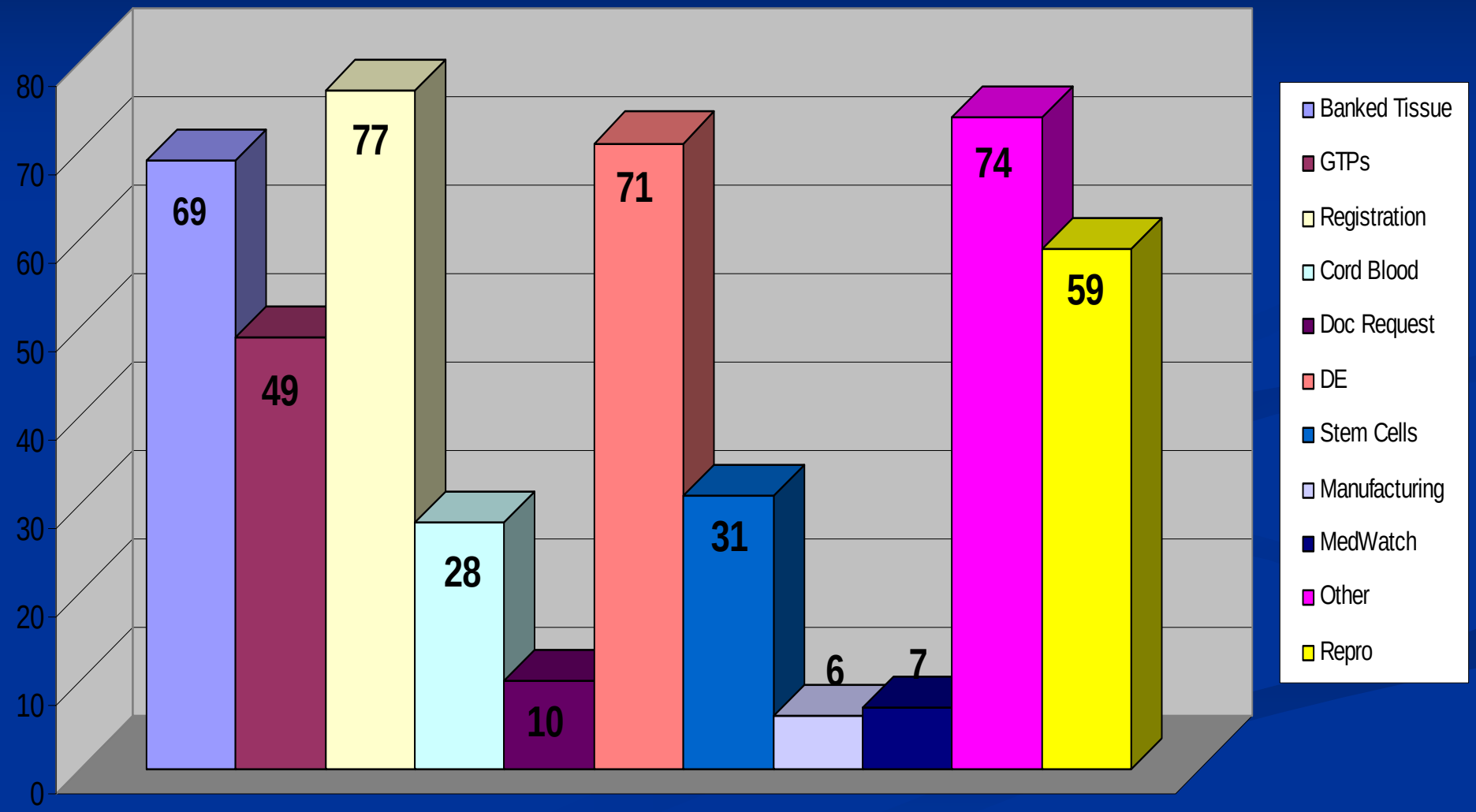
Outreach – Questions

- CBER's Office of Communication, Training and Manufacturers Assistance (OCTMA) receives questions from industry, health care providers, consumers, others
- Manufacturers Assistance - matt@cber.fda.gov or call 800-835-4709 or 301-827-1800

Type of Inquirer - Tissue



Tissue Inquiries - 5/25/2005 to 1/17/2006



OCTMA Inquiries

- OCTMA staff responsible for fielding calls attend FDA HCT/P training and participate in a variety of HCT/P issues
- For "new" issues, questions transmitted to OCTGT, OCBQ and/or OBE contacts.
- Repetitive inquiries (same issue) or inquiries that raise interesting policy issues →

Tissue Policy Team (TPT)

- TPT consists of CBER representatives in four CBER Offices, CDRH and the Center Director's Immediate Office
- Purpose: To identify the need for further rulemaking and policy development, and implement

Tissue Safety Team (TST)

- TST consists of CBER representatives from four CBER Offices and the Center Director's Immediate Office; liaison with ORA, CDC, etc. as needed
- Purpose: To coordinate responses to reports of HCT/P adverse reactions, and to develop procedures to facilitate rapid and comprehensive responses by FDA
- CBER procedure (SOPP 8508) implemented February 2005 (http://www.fda.gov/cber/regsopp/8508.htm)

Rule Changes: Interim Final Rule

- Published May 25, 2005
- Opportunity to comment until August 23, 2005
- Action in response to comments from affected interested persons regarding the impracticability of complying with certain regulations as they affect particular HCT/Ps

Interim Final Rule

- Changes to:
- 1271.55(a)(1) – adds first and second degree blood relatives to the exception to the prohibition to include donor's name to accompanying records
- 1271.80(b) – revised timing of specimen collection 30-days before recovery to include bone marrow not excepted under 1271.3(d)(4) and oocytes

Interim Final Rule cont…

- 1271.90 – adds (a)(4) to include an exemption from screening and testing for cryopreserved embryos from sexually intimate donors that are later intended for directed or anonymous donation.
  - If appropriate screening and testing performed on the donors after cryopreservation and before transfer – new labeling requirement 1271.90(b)(6) applies. If not, labeling per 1271.90(b)(2) and (3) required.

Interim Final Rule cont…

- Additional clarification to 1271.90(b) for labeling of other HCT/Ps excepted from DE determination; autologous cells and tissues, and reproductive cells and tissues donated by a sexually intimate partner.
- Clarification of 1271.90(b)(3) that cells and tissues for autologous use do not require the label "Advise patient of communicable disease risk."

Interim Final Rule cont…

- 1271.370(b)(4) – revised to state that if applying the applicable warnings to the container is physically impossible, then the labeling must accompany the HCT/P.
- Next steps:
  - Comments and questions have been received and are under review at FDA.
  - Publication of a final rule which will address the comments and questions

Rule Changes: Direct Final Rule and Associated Guidance; Phase 1 GMP

- January 12, 2006, Direct Final Rule and companion Proposed Rule on display (published in FR on January 17, 2006); associated guidance issued.
- DFR and PR "Current Good Manufacturing Practice Regulation and Investigational New Drugs," open for comment for 75 days; DFR effective 135 days after FR publication unless significant adverse comments received.
- "Draft Guidance for Industry – INDs - Approaches to Complying with CGMP During Phase 1," open for comment for 90 days.

Rule Changes: Direct Final Rule and Associated Guidance; Phase 1 GMP

- Rule adds 21 CFR 210.2(c), exempting investigational Phase 1 drugs from Part 211 as long as the product has not been made available for Phase 2 or 3
  - "Statutory GMP" applies – Section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act.
- Guidance provides FDA current thinking on complying with statutory GMP for production of Phase 1 IND materials

Inspection Program

- 250 inspections planned for FY06
- New Compliance Program finalized and implemented July 1, 2005
- http://www.fda.gov/cber/cpg/cpg.htm
- Objective: To assess whether all HCT/Ps are mfr in accordance with 21 CFR 1271, and to prevent the introduction, transmission, spread of communicable disease.

Inspection Program – cont.

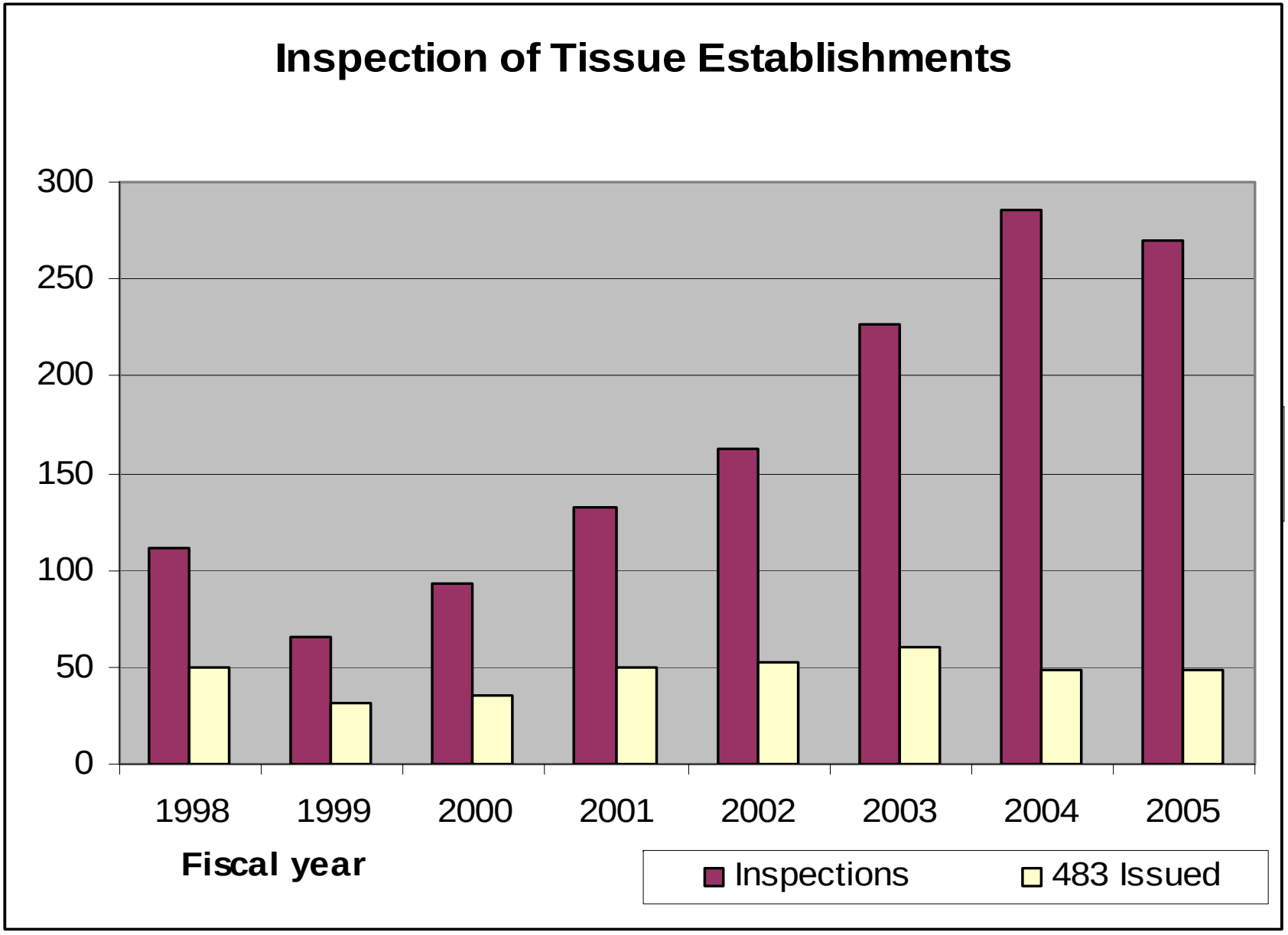
- HCT/P CP objectives accomplished by:
  - Providing procedures for conducting inspections
  - Identifying non-compliance while encouraging voluntary compliance
  - Providing regulatory & administrative information
  - Establishing an inventory of active HCT/P mfrs
  - Taking appropriate enforcement measures

Inspection Program – cont.

- Risk-based selection criteria:
  - Firms whose last FDA inspection was classified OAI (official action indicated)
  - Firms for which FDA has received information about potential violations

Inspection of Tissue Establishments

FY	# Inspections	FDA-483's Issued
1994-97	111	55 (50%)
1998	111	50 (45%)
1999	65	31 (47%)
2000	93	36 (39%)
2001	132	50 (39%)
2002	163	53 (33%)
2003	227	60 (26%)
2004	285	48 (17%)
2005	270	49 (18%)


Inspection of Tissue Establishments
300
250
200
150
100
50
0
1998
1999
2000
2001
2002
2003
2004
2005
Fiscal year
Inspections
483 Issued

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…."

Top Inspectional Observations FY2005 – (1270 and 1271 cites)

- (35) Failure to prepare, validate, or follow written procedures for prevention of infectious disease contamination, cross-contamination during processing
- (24) Failure to prepare, or follow written procedures for all significant steps for obtaining, reviewing, assessing the relevant medical records of a donor
- (18) Failure to maintain records which are accurate, indelible, legible

More Observations FY05 (cont.)

FY2005 – (1270 and 1271 cites)

- (15) Records fail to identify the person performing the work, the date the work was performed and the particular tissue involved
- (15) Records fail to include documentation of destruction or other disposition of human tissue.
- (11) Failure to prepare and/or follow written procedures for designating and identifying quarantined tissue
- (9) Tissue intended for transplantation was not accompanied by a summary or copies of the donor's relevant medical records

More Observations FY05 (cont.)

FY2005 – (1270 and 1271 cites)

- (9) Procedures for all steps performed in the testing, screening, determining of donor eligibility of HCT/Ps were not established, maintained, and followed
- (9) Records fail to include documentation of receipt and/or distribution of human tissue
- (8) Failure to test donor specimens for communicable viruses using FDA licensed donor screening tests in accordance with manufacturers' instructions

Tissue Inspections May 25, 2005 through December 31, 2005

Types of HCT/P establishment	# Inspections performed	# FDA-483s issued
Reproductive tissues	13	2 (15%)
Cord blood stem cells Peripheral Blood stem cells	14	6 (43%)
All other HCT/Ps (e.g. musculoskeletal, ocular, OPO, distributors)	137	23 (17%)
Total	**164**	**31 (19%)**

Top Inspectional Observations May 25, 2005 through Dec. 31, 2005 (1271 cites)

- (9) Procedures for all steps performed in the testing, screening, determining of donor eligibility of HCT/Ps were not established, maintained, and followed [1271.47(a)]
- (4) Donors were not screened by a review of relevant medical records for risk factors, clinical evidence of communicable disease agents and diseases [1271.75(a)(1)]
- (4) The quality program has not established and maintained appropriate monitoring systems [1271.160(b)(5)]

Observations May 25, 2005 through Dec. 31,2005(Cont.) (1271 cites)

- (3) The quality program has not ensured the proper training and education of personnel involved in core GTP activities [1271.160(b)(4)]
- (3) Procedures appropriate to meet core CGTP requirements for all steps that you perform in the manufacture of HCT/Ps were not established, maintained, and implemented [1271.180(a)]

Observations May 25, 2005 through Dec. 31, 2005 (cont.) (1271 cites)

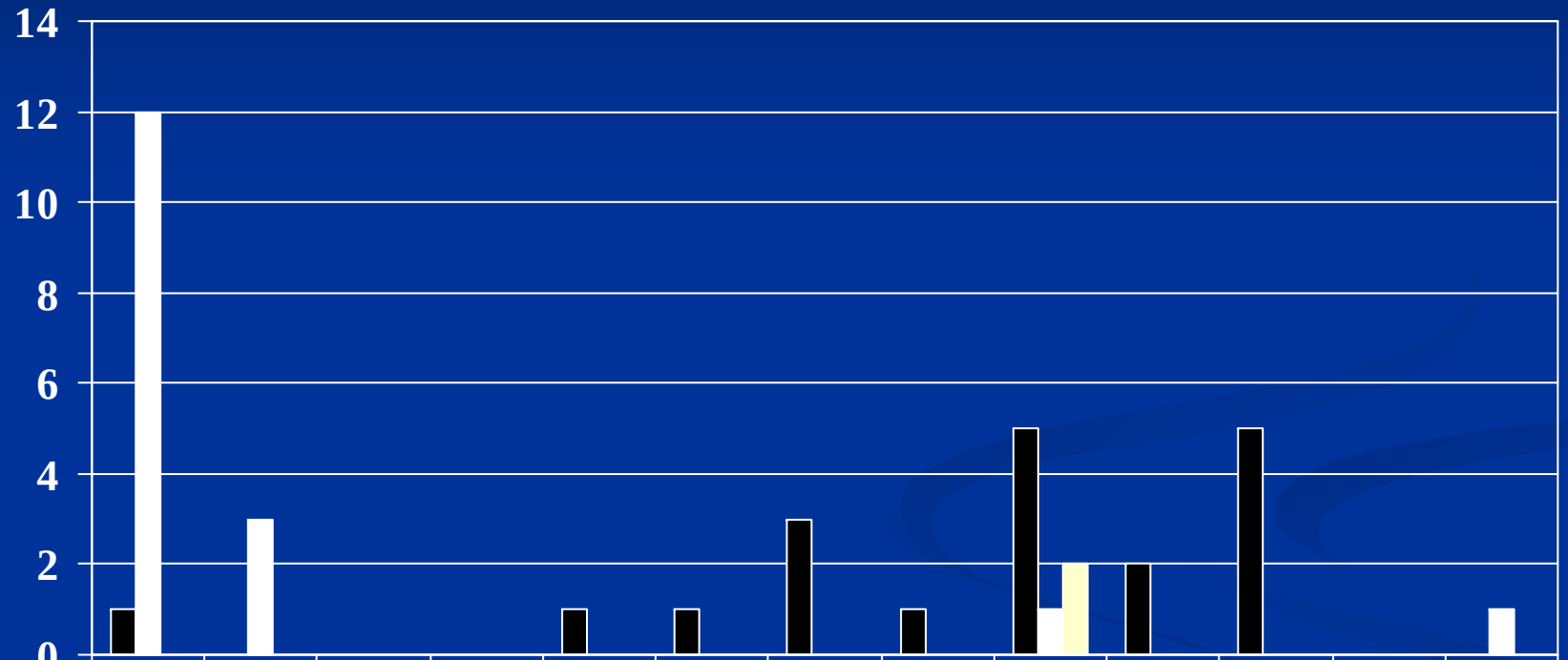
- (3) A standard operating procedure for the release of HCT/Ps from donors that test reactive for CMV was not established, maintained, implemented [1271.85(b)(2)]
- (3) Environmental conditions are not monitored when such conditions could cause contamination, cross contamination of HCT/Ps or equipment [1271.195(c)]

Discussion items – not cited- May 25, 2005 through Dec. 31, 2005

- Need to have complaint files and procedures
- Recordkeeping practices for receipt, distribution and tracking were not adequate
- Accompanying records need to have statement that viral marker testing was done in a CLIA certified lab
- Record retention pertaining to particular HCT/P must be retained at least 10 years after the date of administration or the date of HCT/P distribution, disposition, or expiration, whichever is latest

Tissue Regulatory Actions

(FY06 as of 11/30/2005)



	FY94	FY95	FY96	FY97	FY98	FY99	FY00	FY01	FY02	FY03	FY04	FY05	FY06
WL's	1	0	0	0	1	1	3	1	5	2	5	0	0
Orders	12	3	0	0	0	0	0	0	1	0	0	0	1
Other*	0	0	0	0	0	0	0	0	2	0	0	0	0

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.
- FDA continues to investigate BTS' activities and to work cooperatively with tissue processors and federal, state and local authorities
- Further action will be taken as needed.

BTS - Chronology

- Voluntary recalls initiated immediately by tissue processors and BTS (September 30 - October 14, 2005); posted on CBER's website
  - FDA carefully monitoring to account for all tissue distributed
- FDA inspection of BTS and several funeral homes that provided potential donors for recovery – October 4- 27, 2005.
- FDA Information Paper – October 26, 2005

www.fda.gov/bbs/topics/NEWS/2005/NEW01249.html

Information Paper

- FDA provides information on investigation of BTS
- FDA and CDC believe the risks from the tissues are likely low because the tissues were routinely processed using methods that help to reduce the risk of infectious disease; however, the actual infectious risk is unknown.
- Processors have already recalled tissue and working cooperatively with the FDA to ensure physicians are notified
- FDA and CDC recommend that physicians inform their patients and offer to provide patients access to appropriate infectious disease testing.

BTS Order

- 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
- Press release with link to Order

http://www.fda.gov/bbs/topics/news/2006/NEW01309.html

BTS Order

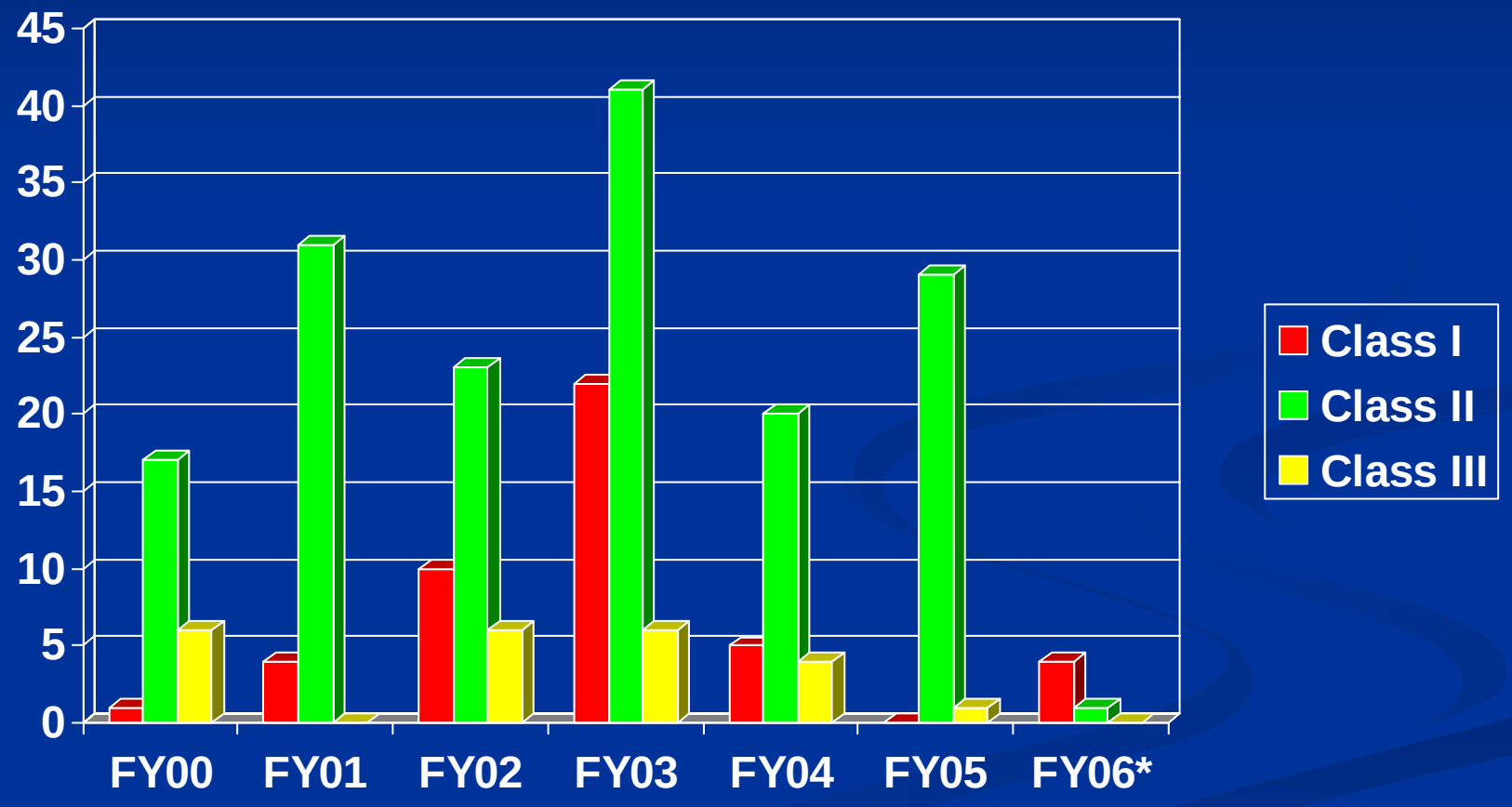
- The order alleges that FDA's inspection uncovered serious violations of the regulations governing donor screening and record-keeping practices, and:
  - Failure of the firm to follow its own SOPs;
  - Failure to recover HCT/Ps in a manner that does not cause contamination or cross-contamination;
 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

Tissue Recalls Classified

*FY06 as of 1/18/06



Classified Recalls FY 2004

	Tissue	CBER Total (all products)
FY 04 Class I	5	5
FY 04 Class II	20	1523
FY 04 Class III	4	530

FY04 Class I Tissue Recalls (5)

- Tissue + for group A Strep, recip got infection
- Tissue + for Bacteroides, recip got infection
- Donor HCV PCR + (firm informed after distribution
- Donor HCV + by EIA and PCR (likely sample mix up)
- Confirmed + HBsAg (lab reported as negative first)

Classified Recalls
FY 2005

	Tissue	CBER Total (all products)
FY 05 Class I	0	1
FY 05 Class II	29	1848
FY 05 Class III	1	601

RECALLS: FY 2005

- Before 5/25/05
  - 0 Class I Recalls (reasonable probability that use or exposure will cause serious adverse health consequences or death)
  - 22 Class II Recalls (use or exposure may cause temporary or medical reversible adverse health consequences or probability of serious adverse health consequences remote)
  - 1 Class III Recall (use or exposure not likely to cause…)

RECALLS: FY 2005

- After 5/25/05 – 7 Class II Recalls
  - 4 were for products recovered prior to 5/25
  - 3 for products recovered after 5/25
    - 2 donor history ineligible
    - 1 not quarantined and sent prior to completion of eligibility determination

Classified Recalls
FY 2006 (as of 1/18/06)

	Tissue	CBER Total (all products)
FY 06 Class I	4	4
FY 06 Class II	1	252
FY 06 Class III	0	78

FY 2006 Class I Tissue Recalls

(as of 1/18/2006)

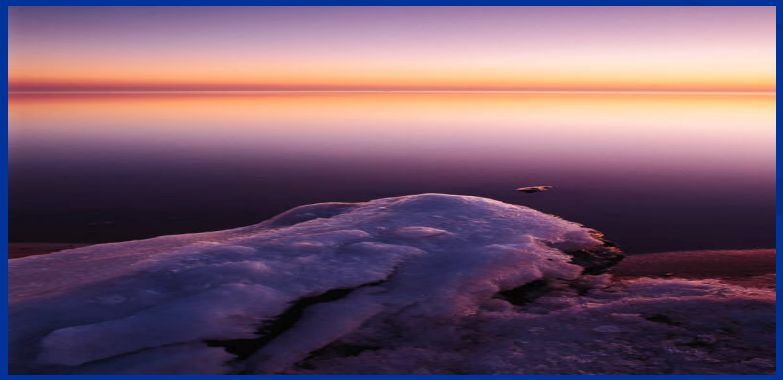
- **Biomedical Tissue Services, Ft. Lee, New Jersey**
  - Human tissue, recovered from donors without adequate donor eligibility determinations, was distributed.
  - Recalled tissue collected from 761 donors
- Subrecalls performed by tissue processors:
  - LifeCell (Branchburg, New Jersey); Tutogen Medical (Alachua, FL); Regeneration Technologies (Alachua, FL); Central Texas Blood & Tissue (Austin, TX), and Lost Mountain Tissue Bank (Kennesaw, GA)

Other activities

- Imports
  - Working with the Division of Import Operations; instructions provided to FDA import staff regarding reproductive and hematopoietic stem/progenitor cell imports
  - Continued work with the industry regarding import of hematapoietic stem/progenitor cells
  - Continued development of instructions to FDA import staff working with our Office of Regulatory Affairs

Other activities, cont..

- Will continue work on regulatory guidance and policy development
- Will continue internal and external outreach and welcome stakeholder input
- Will continue to monitor inspectional outcomes
- Will continue to monitor HCT/P deviation and Adverse Reaction reports and develop guidance

“The best thing about the future is that it comes only one day at a time.”

Abraham Lincoln (1809-1865)