HCT/P Compliance Update

4th Annual FDA and the Changing Paradigm for HCT/P Regulation

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U.S. Department of Health and Human Services

Food and Drug Administration

Summary

- Inspections and actions by the numbers
- Regulatory action citations
- Recalls
- HTTF and Recovery Blitz Update

FY07 HCT/P Inspections Accomplished

Type of HCT/P establishment	**# Inspections Accomplished**	**Hours/ Inspection**
Reproductive tissues	164	44
Cord blood stem cells Peripheral blood stem cells	18	26
All other HCT/Ps (e.g. musculoskeletal, ocular, recovery, distributors)	249	50
Total	**426***	

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

FY07 HCT/P Inspection Classifications

Type of HCT/P establishment	NAI	VAI	OAI
Reproductive tissues	111	45	7
Cord blood stem cells Peripheral blood stem cells	15	3	0
All other HCT/Ps (e.g. musculoskeletal, ocular, recovery, distributors)	182	65	2
Total **(does not include 1 blank classification)**	308	113	9

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

FY07 HCT/P Inspection Results

- Approx. 30% of HCT/P inspections resulted in issuance of Form FDA-483s

- Regulatory Actions Issued
  - 3 Warning Letters (1 test lab, 2 repro)
  - 2 Untitled Letters (both repro)

Consideration for Action

- Investigator does initial assessment of inspection; may designate “Official Action Indicated,” if, in his/her judgment, warrants further action
- Supervisory review – if concur – send to Compliance Branch
- If Compliance Branch agrees – forward recommendation with draft action to relevant program Center(s)

Consideration for Action

- Center Compliance reviews recommendation and draft action:
  - Nonconcur or disapprove – document reasons
  - Concurrence – document concurrence; suggest edits – forward to Office of Chief Counsel(OCC)
- OCC reviews draft action
  - Nonconcur – document reasons
  - Concur – Original district issues

Your Response

- If, at any time during review your FDA-483 response is received; the review clock stops while it is given full consideration. It will also be reviewed for consideration at all stages.

Warning Letters

- Require a company response
  - You should apply to all sites
- Other government agencies notified
- Posted on the website
  - Pilot to request responses be posted began September 22, 2003 (Federal Register notice published June 23, 2003 Vol. 68 Number 120)
- Inadequacies in your response will be addressed
- Usually FDA's last attempt to get company's attention before enforcement action

Untitled Letters

- Communication to the industry on concerns
- May ask for a response
- Other federal agencies not advised
- No warning statement
- Same review as Warning letter,i.e. center and OCC

FY07 HCT/P Regulatory Actions Deviations Cited

- Failure to establish and maintain donor screening and testing procedures (1271.47(a))
  - Donor eligibility forms not available or incomplete
  - No written procedures for donor screening/testing
- Failure to ensure appropriate corrective actions (1271.160(b)(3))
  - Corrective actions implemented that are contrary to regulatory requirements

FY07 HCT/P Regulatory Actions Deviations Cited (2)

- Failure to adequately determine and document donor eligibility (1271.50)
  - No documentation of eligibility determination
  - Donor determined eligible before testing complete
- Failure to adequately screen donor (1271.75)
  - Relevant medical records not reviewed/retained
  - Abbreviated screen not performed

FY07 HCT/P Regulatory Actions Deviations Cited (3)

- Donor Testing Deviations:
  - Donor tested positive, not considered ineligible (1271.80(d)(1))
  - Not using donor screening tests (1271.80(c))
  - Not following manufacturer's instructions (1271.80(c))
    - IR not repeated in duplicate
    - Tested into compliance
  - Incorrect timing of specimen collection (1271.80(b))
  - Not testing for all relevant communicable diseases (1271.85(c))
    - Chlamydia, Neisseria

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

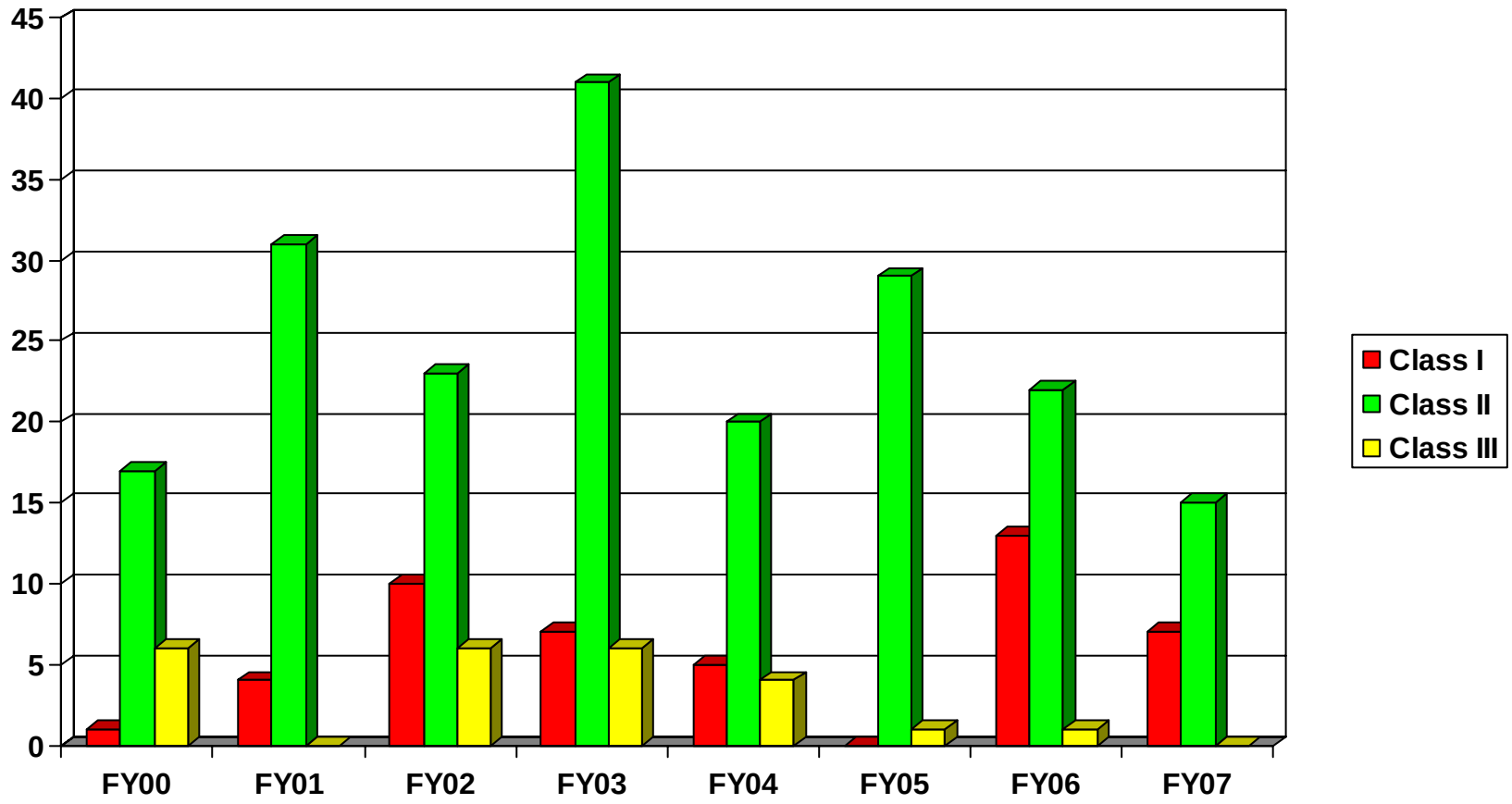
FY 2007 Class I HCT/P Recalls

- Donor Referral Service (DRS), Raleigh, NC
  - HCT/Ps, recovered from donors without adequate donor eligibility determinations, were distributed.
- Sub-recalls performed at several processors
- 5 of 7 Class I recall events related to HCT/Ps recovered by DRS

FY 2007 Class I HCT/P Recalls Other Reasons for Recall

- Recipients of companion soft tissue reported infection with Enterobacter faecalis
- Recipient of associated donor tissue reported infection with Clostridium septicum

HCT/P Recalls Classified



Update on Human Tissue Task Force and Recovery Blitz

Summary

- Highlights of the June 12, 2007, report from the Human Tissue Task Force (HTTF)
- Additional information on the overall compliance status of the industry and industry practices affecting the risk of communicable disease transmission

HTTF

- Formed in August 2006, as part of the Agency's efforts to evaluate and, where needed, strengthen its risk-based system for regulating human cells, tissues, and cellular and tissue-based products (HCT/Ps)
- The primary goal of the HTTF was to assess challenges that had occurred in implementation of the new system and to identify any additional steps needed to further protect the public health by preventing the transmission of communicable disease while assuring the availability of safe products.

Members

- Office of Regulatory Affairs (ORA)
- Center for Biologics Evaluation and Research (CBER)
- Office of the Commissioner

Areas Considered

- Inspection and Compliance Activities
  - Additional information
- Partnering, Leveraging, Education, and Outreach
- Adverse Reaction Reporting and Analysis
- Additional Regulations and Guidance Development
- The Science of Tissue Safety

Inspections and Compliance Activities

- 2023 registered establishments; 859 manufacture from non-living donors
- From October 1, 2006-March 31, 2007, 153 inspections of domestic musculoskeletal recovery establishments were conducted.
- Assignment designed by CBER and ORA to detect inaccuracies and deficiencies in records like those noted during the Biomedical Tissue Services and Donor Referral Services inspections and to collect information on industry practices affecting the risk of communicable disease transmission

Summary of Findings

- Though deviations from the regulations were noted during some of the inspections, there were no major inaccuracies or deficiencies observed in records
- No inspections resulted in regulatory action
- Some firms were out of business, were not performing recovery, or did not store donor records on site
- 134 establishment inspection reports were reviewed to assess the overall compliance status of the industry
- 125 of the reports were further analyzed to assess industry practices affecting the risk of communicable disease transmission
- Some of the results of these assessments are summarized in this presentation

Organization and Operations
Recovery Firm Size

- Large (>50 employees) – 22% of establishments
  - Most also procure organs, some also process HCT/Ps
- Medium (10-50 employees) – 48%
  - Some organ procurement, many also process HCT/Ps
- Small (<10 employees) – 30%
  - Most focus on recovery operations

Organization and Operations

Donor recovery volume

- Number of donors recovered
  - HCT/Ps recovered from approx. 43,000 donors in CY 2005
- Recovery volume by firm size
  - Large firms recovered 54% of the donors
  - Medium firms 34%
  - Small firms 12%
- Each establishment’s rate of recovery generally stable in previous 3 years

Organization and Operations
Recovery locations

- Most common recovery locations and percentage of recovery establishments that use the locations*
  - Hospital OR – 93%
  - Funeral homes – 59%
  - Medical examiner/coroner – 59%
  - Morgue – 26%
  - Dedicated recovery suite – 18%

*Most establishments recover at more than one location type

- Most establishments have contract, agreement, or arrangement with recovery locations
- All establishments had procedures related to control of aseptic conditions during recovery

Organization and Operations
Donor eligibility (DE) determinations

- No recovery establishments are performing final DE determination
- All final DE determinations by processors
- Recovery establishments may assemble DE related records and send to processor for assessment

Organization and Operations

Process flow and organizational relationships

- Dissemination of HCT/Ps, test samples, and information can be complex
- Multiple establishments often involved
- Inspections increased our understanding of the relationships

Compliance Information

FDA Form 483s
(List of Observations)

- For all recovery establishments:
  - 35/134 inspections or 26% resulted in the issuance of an FDA Form 483
- For establishments with prior inspections:
  - 28/118 inspections or 24% resulted in the issuance of an FDA Form 483
- For establishments with no prior inspections:
  - 7/16 inspections or 44% resulted in the issuance of an FDA Form 483
- There was no significant difference based on the size of the establishment

Compliance Information

Most Common Observations of Deficiencies

- 1271.200 – Equipment cleaning, maintenance, calibration
- 1271.270 – Records
- 1271.180 and 47 – Core CGTP and DE procedures
- 1271.190 – Facility cleaning and sanitization
- 1271.160 – Quality program

HTTF Recommendations: Inspections

- Recommendations for inspectional goals and priorities made
- Resources needed include: training, time, planning, human and financial resources

Partnering, Leveraging, Education, and Outreach

- Federal Partners: CDC, HRSA, FTC
- States
- Eye Banking and Tissue Industry
- Academic and Professional Organizations

HTTF Recommendations

- Partnering, leveraging, education, and outreach activities, could expand, but such expansion would require additional resources.
- Such activities could enable: improvements to our communication network with state and federal regulatory partners, sharing of information, and greater knowledge of industry operations and clinical practices. Additional resources could also allow enhanced communication with academic and professional organizations.

Adverse Reaction Reporting and Analysis

- Reviewed FDA's current procedures for adverse reaction receipt, analysis and follow-up utilized by the Tissue Safety Team (TST).
- Enlisted the consultative services of a nongovernmental academic infectious disease specialist with extensive clinical experience to identify opportunities to improve procedures for investigation, classification, and analysis of adverse reaction reports related to tissue transplants.

HTTF Recommendations

- With current resources:
  - Refine the activities of the TST
  - Continuing interactions with outside experts
  - Coordinating with CDC regarding the proposed Transplantation Transmission Sentinel Network (TTSN) project to assure that the TTSN complements FDA's existing surveillance system, and
- Other actions may be undertaken with additional planning and/or resources

Update

- With CDC and FDA's Center for Devices and Radiological Health and Office of Regulatory Affairs, CBER co-sponsored "*Processing of Orthopedic, Cardiovascular, and Skin Allografts Workshop,*" October 10-11, 2007
- Health care providers, scientists and industry participated to share knowledge and experiences regarding technologies and methods to enhance tissue safety.
- In process of evaluating lessons learned

Additional Guidance and Policy Considerations

- Issued guidance clarifying responsibilities between establishments and contract establishments
- In process of drafting Current Good Tissue Practice (CGTP) guidance
- Other issues under consideration:
  - Tracking to the recipient
  - DE determination and original record review
  - Auditing contractors

The Science of Tissue Safety

- Tissue microbiology program
- Critical path activities and partnerships to evaluate and identify manufacturing practices that reduce infectious disease risks

HTTF: Future Role

- Issues that require cross-agency, multidisciplinary perspective
- Track implementation of recommendations
- Discuss emerging issues and opportunities

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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Questions?