

# Challenges in Biologics Compliance

*2<sup>nd</sup> Annual FDA Inspections Summit*

*October 23, 2007*

*Mary Malarkey, Director*

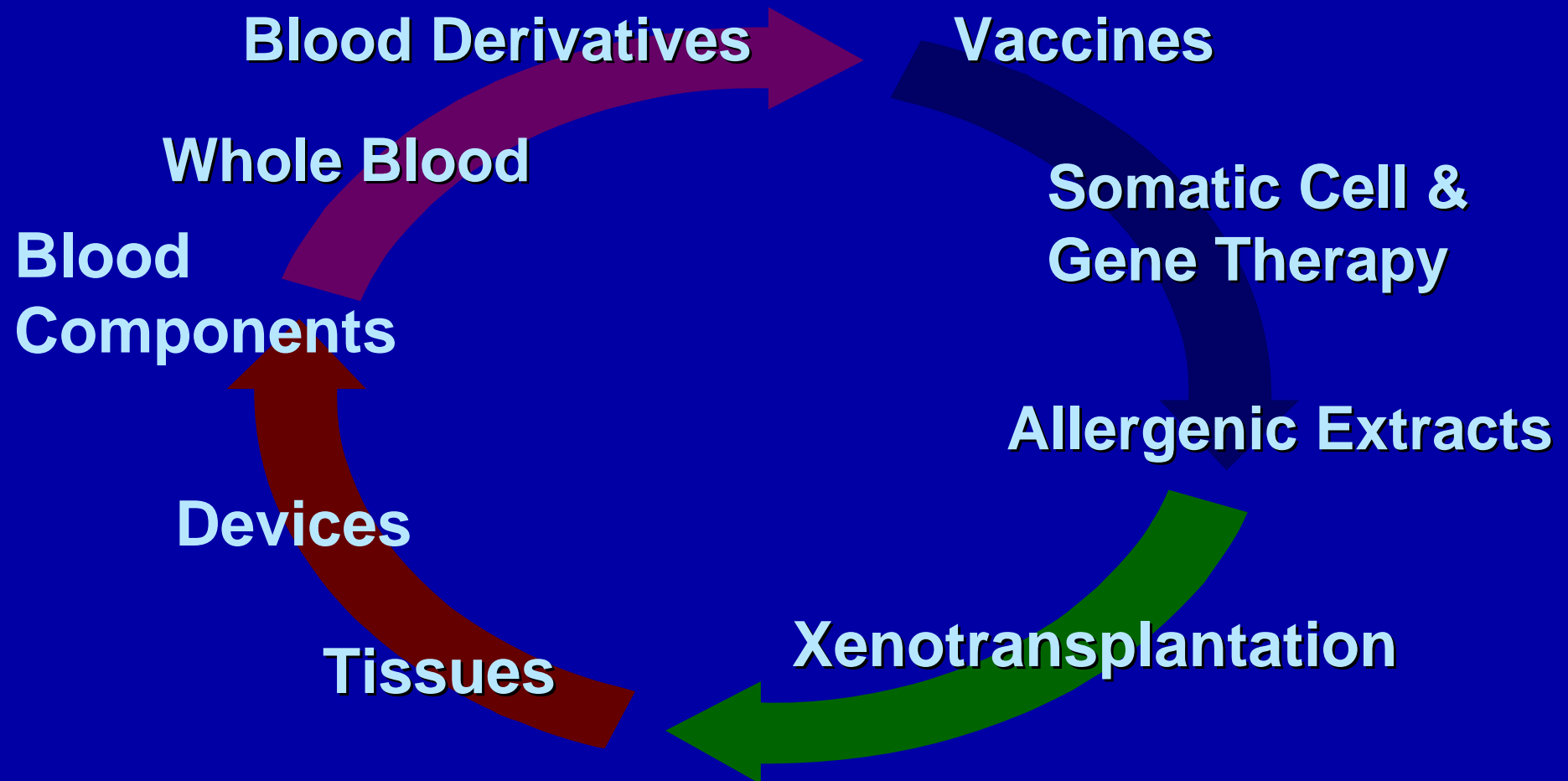
*Office of Compliance and Biologics Quality*



U.S. Department of Health and Human Services

Food and Drug Administration

# Critical Products for Public Health, National Preparedness & 21<sup>st</sup> Century Medicine



# 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**

# Challenges?

- Many challenges exist – covered today?
- General – manufacturing quality and safety
- Recalls
- Human, Cells, Tissue and Cell and Tissue-Based Products (HCT/Ps)
- Compliance related to biological drugs and devices
- Pandemic Influenza

# Manufacturing and Quality

- Enhance risk-based scientific oversight and quality of manufacturing throughout the product life cycle

# Manufacturing and Quality

- Continue efforts to modernize biologic and drug regulations and where possible to harmonize with other regulatory authorities
  - 21 CFR Part 600-680
  - 21 CFR Parts 210-211
- Enhance scientific tools and assessment for manufacturing – CBER research
  - Associate Director for Manufacturing Science
    - OCBQ
- Continue GMP Outreach to vaccine and
- other industries

# **CBER's Safety Teams**

- **Tissue (2004), Blood (2006), Vaccine (2007)**
  - **Multidisciplinary and collaborative – each includes product, manufacturing, safety, clinical, compliance, and communication experts – all share common data**
  - **Meet at least monthly, IOD participates, entire team also meets quarterly with Center Director/Deputy – can be immediately convened in any emerging/urgent situation**
  - **Structured interfaces with ORA, CDC, others as appropriate**
- **Goals/accomplishments:**
  - **Proactively and rapidly identify and address significant ongoing and emergent safety issues**
  - **Serve as focus for developing and implementing longer term priorities, innovative practices and collaborations, and quality improvement**
  - **Enhance internal and external communication and collaboration (including public, rest of FDA, CDC, HRSA, international/WHO etc.)**

# FY06 - Recalls

<b>Product</b>	<b>FY03</b>	<b>FY04</b>	<b>FY05</b>	<b>FY06</b>
Blood	1555	1773	2130	1633
Source Plasma	203	242	263	150
Derivative	0	2	3	0
IVD	13	3	8	4
Vaccine	1	2	0	1
Therapeutic	5	0	0	0
Allergenic	1	1	0	0
Device	16	6	16	17
Tissue	70	29	30	36
<b>TOTAL</b>	<b>1864</b>	<b>2058</b>	<b>2450</b>	<b>1841</b>

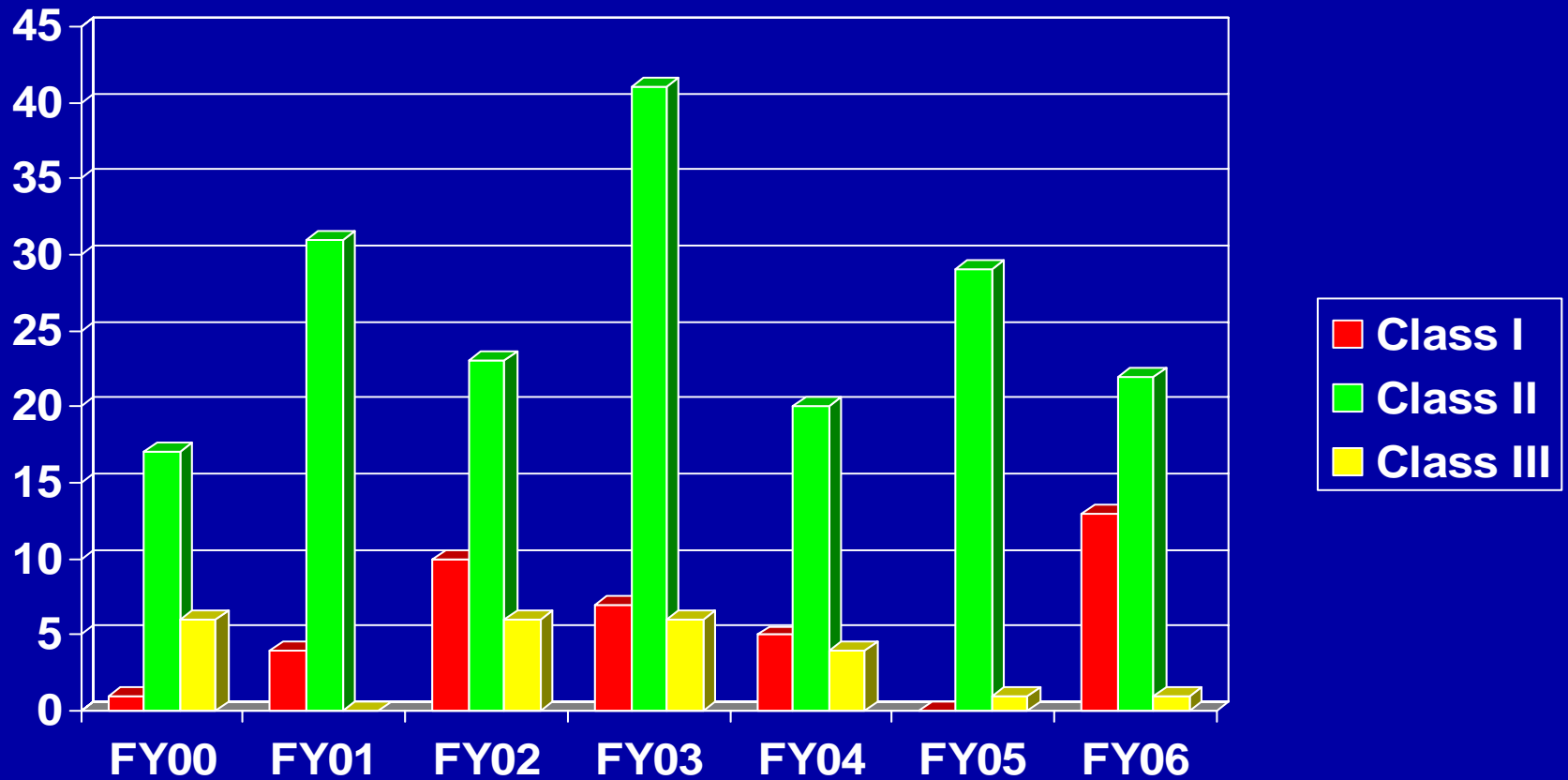


# Classified Recalls

## FY 2006

	HCT/Ps	CBER Total (all products)
FY 06 Class I	13	13
FY 06 Class II	22	1377
FY 06 Class III	1	451

# HCT/P Recalls Classified



# FY 2006 Class I HCT/P Recalls

- Biomedical Tissue Services (BTS), Ft. Lee, New Jersey
  - HCT/Ps, recovered from donors without adequate donor eligibility determinations, were distributed.
  - Recalled HCT/Ps collected from 761 donors
- Subrecalls performed at several processors
- 9 of 13 Class I recall numbers related to HCT/Ps recovered by BTS

# FY 2006 Class I HCT/P Recalls

## Other Reasons for Recall

- Related tissue + for microorganisms
- Recipient of related tissue reported infection with *Clostridium septicum*
- Donor HCV NAT + (firm informed after distribution)
- Donor HCV + by EIA and NAT (results attributed to wrong donor)

# **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](http://www.fda.gov/cber/compl/bts013106.htm)**

# Updated Notification

- Issued March 2, 2006  
[www.fda.gov/cber/safety/bts030206.htm](http://www.fda.gov/cber/safety/bts030206.htm)
- New information that calls into question the reliability of some of the donor blood samples submitted for communicable disease testing from BTS tissue donors. In some instances, blood samples did not come from the same donor as the linked tissues
- Results of communicable disease tests obtained from the blood sample may not correctly reflect the status of the donor

# 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.



# **Donor Referral Services (DRS) Order to Cease and Retain HCT/Ps**

- **Immediately cease manufacturing operations and retain HCT/Ps.**
- **To DRS and its Owner, Philip Guyett**
- **FDA determined that the violations uncovered at DRS, because of their serious nature, constitute a danger to health.**
- **Order to Cease Manufacturing and to Retain HCT/Ps issued August 18, 2006**
- **[www.fda.gov/cber/compl/drs081806.htm](http://www.fda.gov/cber/compl/drs081806.htm)**

# DRS Order

- **The order alleges that FDA's inspection uncovered serious violations of the regulations governing donor screening and record-keeping practices, and:**
  - failure to create and maintain accurate records;
  - failure to establish and maintain SOPs for all steps performed in manufacturing of HCT/Ps;
  - failure to review relevant medical records regarding risk factors for, or clinical evidence of, relevant communicable disease agents and diseases.

# DRS Order

- **FDA found numerous instances where information provided by DRS to a tissue processor was at variance with the death certificates FDA obtained from the state where the death occurred:**
  - **Cause, place, and time of death**
- **FDA continues to investigate DRS working with other federal, state and local authorities**

# DRS Public Health Notification

- August 30, 2006
- FDA and CDC strongly recommending health care providers inform all patients that received tissue initially recovered by DRS and offer access to communicable disease testing
- Distributing firms had already voluntarily recalled tissue in inventory
- Where FDA had previously identified specific cases of concern, the firms cooperated fully in efforts to inform patients and offer testing in those cases

# Human Tissue Task Force (HTTF)

- Formed in August to evaluate effectiveness of new regulations and to identify whether additional steps necessary to strengthen regulatory framework
- Collaborative effort between CBER, ORA and OC
- Final report issued June 12, 2007

[www.fda.gov/cber/tissue/httf07report.htm](http://www.fda.gov/cber/tissue/httf07report.htm)

# HTTF

- 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.

# 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

# HTTF Conclusions: 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 Conclusions

- 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 Conclusions

- 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

# HTTF Conclusions (cont..)

- Sponsored a workshop with CDC and FDA's Center for Devices and Radiological Health on tissue processing, October 10-11, 2007
- Health care providers, scientists and industry participated to share knowledge and experiences regarding technologies and methods to enhance tissue safety.
- Other actions may be undertaken with additional planning and/or resources

# 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



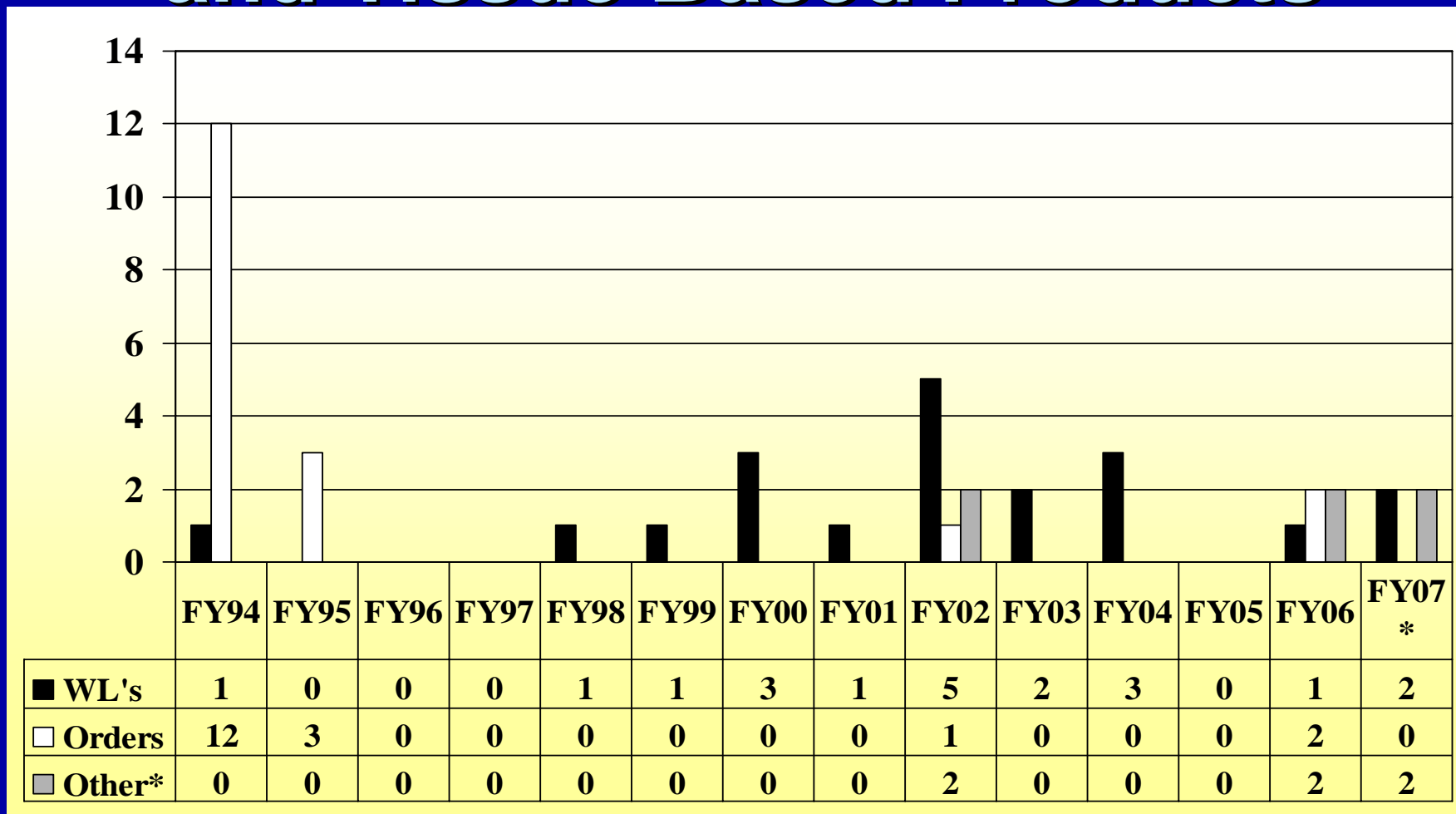
# The Science of Tissue Safety

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

# HTTF: Future Role

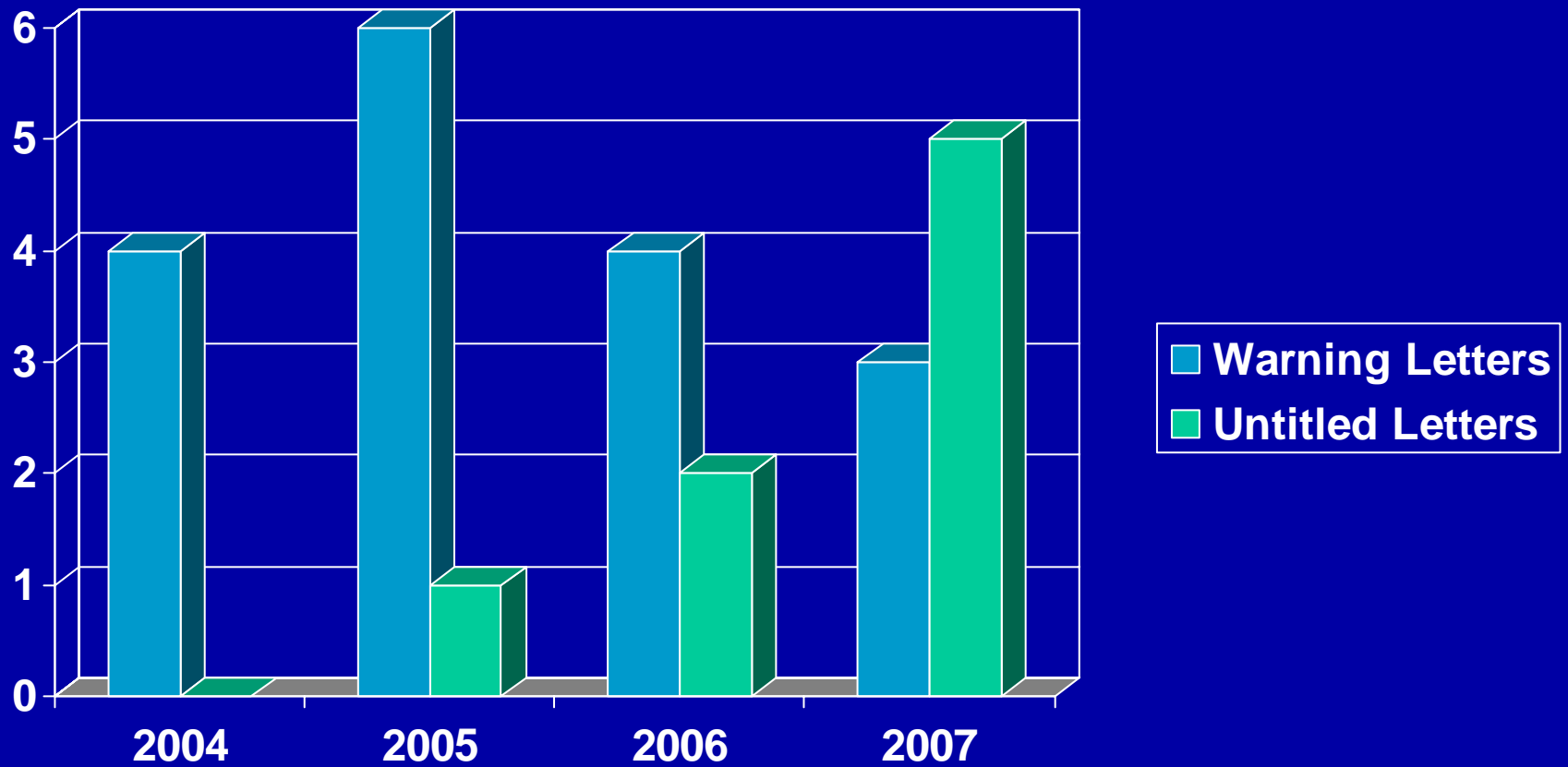
- Issues that require cross-agency, multidisciplinary perspective
- Track implementation of recommendations
- Discuss emerging issues and opportunities

# Human Cells, Tissues and Cellular and Tissue Based Products



\* As of July 31, 2007

# Biological Drug and Device



# 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”
211.100	“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. For example:”
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.”
601.12	“Failure to inform FDA about each change in the production process in that supplements were not submitted for products that were ...”

# 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..”

# Team Biologics

- From the Final Report on the CGMP Initiative (September 2004):

*“The Team Biologics initiatives fully complement the CGMP Initiative’s goals and efforts.”*

# Team Biologics Operations Group

- Outside evaluation
  - Working group established between the Pharmaceutical Quality Research Institute (PQRI) and Team Biologics Operations Group members to develop a survey for industry
  - A contractor gathered survey responses for PQRI maintain anonymity
  - PQRI and Team Biologics members analyzed the blinded results for publication
  - The working group's analysis of the results was be published in the May-June 2007 "PDA Journal"



# Survey Facts

- Surveys sent by PQRI to heads of quality at 163 registered sites
- 42 or 26% responded
- Most responses from therapeutic industry; the least from allergenic industry
- Highest response rate (36%) from plasma derivative industry

# What changes in operations/procedures were made as a result of Team Biologics inspections?

- Across the industry:
  - 67% reported changes in failure investigations and this seemed primary focus for most sites
  - 72% reported changes in production and process controls
  - 61% reported changes in written procedures
  - 39% reported changes in each of the following: management of priorities, training and quality unit activities

**Overall, has the Team Biologics program had an impact (positive, negative or neutral) on your operation? (e.g. regulatory, reputation, business, operations, culture of quality)**

- 68% indicated an overall positive impact
- 13% indicated an overall negative impact
- 19% indicated an overall neutral impact

# What was positive?

- “The program has required a culture of quality that would not have been present...The program has required management to listen to quality and put higher priority on quality’s requests.”
- “Positive: with continuous improvement as a result. We do expect a more risk-based approach in the future, based on implementation of Q8 and Q9.”

# What was negative?

- “Would like to see FDA provide more education for companies and more clear regulations. Providing a citation, then education/interpretation seems like the wrong approach.”
- “Positive and negative. In a positive sense, we are more compliance oriented; however, sometimes good science has suffered because of compliance.”

# Next Steps?

- Team Biologics Operations Group will use survey data and comments to further improve the operations of Team Biologics

# BIMO –Warning Letters

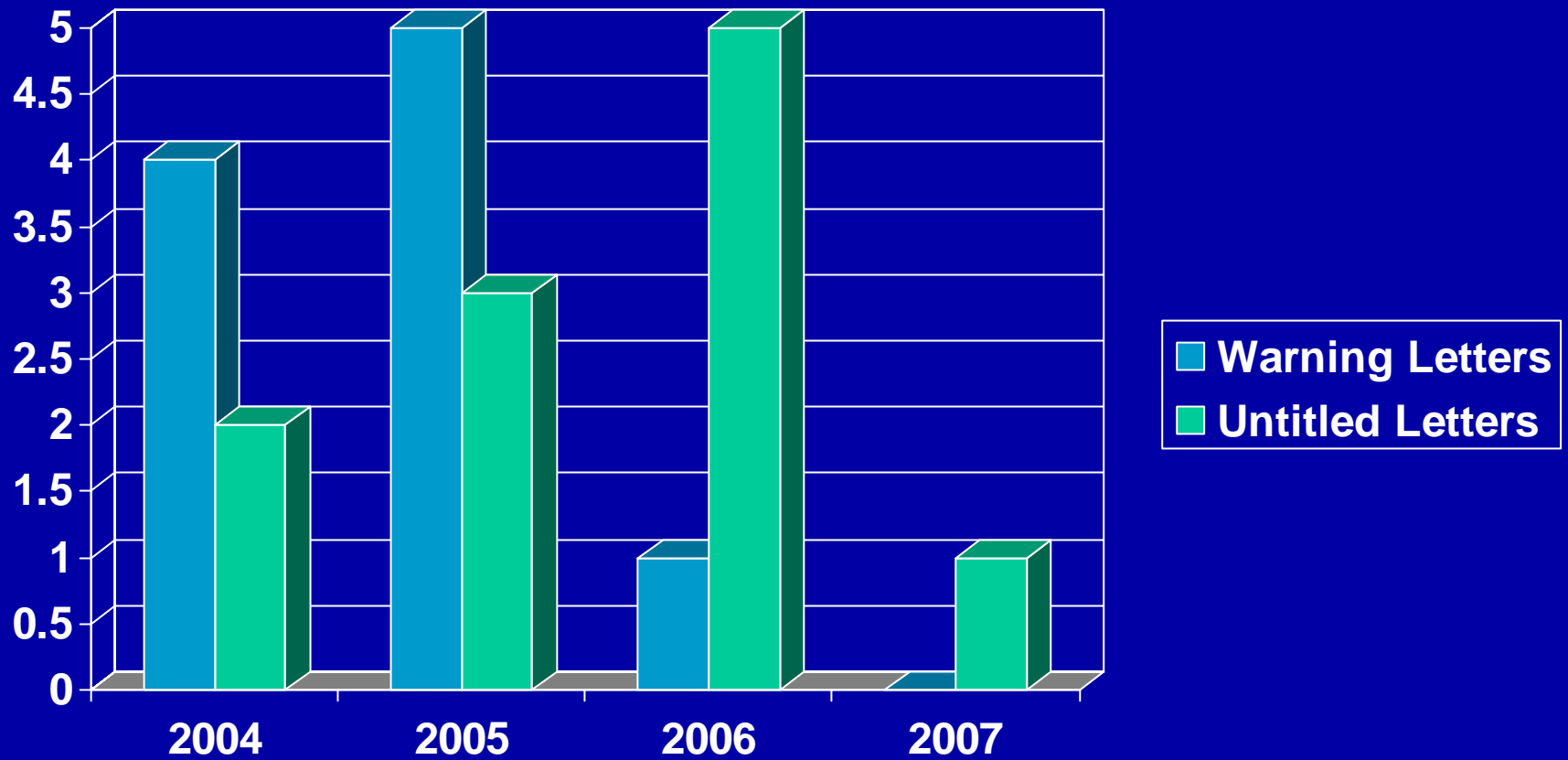
	FY04	FY05	FY06	FY07
Clinical Investigators	4	12	0	3
Sponsors	0	2	1	1
Sponsor- Investigator	1	0	1	0
IRBs	0	0	3	2
GLP	0	0	0	2

# BIMO

- Continued issues with human subject protection; inaccuracies in records and data
  - Sponsors, investigators and IRBs not fulfilling their responsibilities under the regulations
- CBER continues random surveillance to focus on agency priorities and vulnerable populations, e.g. pediatric and elderly



# Internet Surveillance



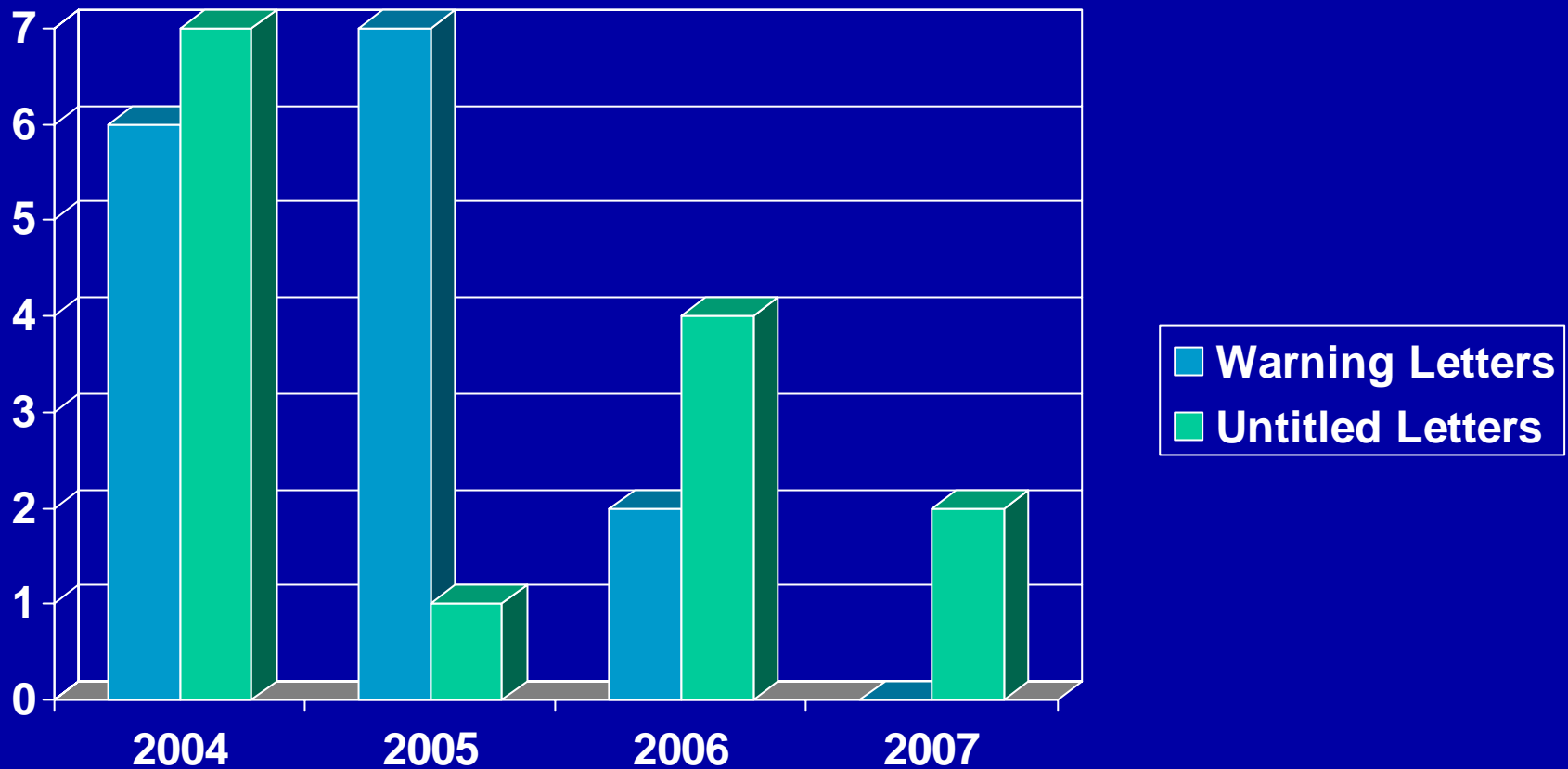
# Internet

- Unapproved HIV tests remain a problem
- Enforcement Working Group under the FDA Pandemic Preparedness Task Force has been looking at products promoted to prevent and/or treat avian influenza:

[www.fda.gov/opacom/backgrounders/problem.html](http://www.fda.gov/opacom/backgrounders/problem.html)

[www.fda.gov/oc/buyonline/buyonlineform.htm](http://www.fda.gov/oc/buyonline/buyonlineform.htm)

# Advertising and Promotional Labeling



# Advertising and Promotion

- Discussion of benefits/efficacy with omission of risk information and/or adequate directions for use [21 CFR 201.100(d)]
- Failure to submit to FDA at the time of dissemination [21 CFR 601.12(f)(4)]

# Pandemic Influenza Update

# Seasonal and Pandemic Influenza Virus Vaccines

- Continued work with licensed and new manufacturers to establish or expand facility capacity; including regular meetings to advise on design of facilities; CGMP
- Encouraging the use of new technologies for production and delivery of influenza virus vaccines
- Annual inspections of influenza virus vaccine manufacturers; facilitation of remediation efforts

# Accomplishments

- Approval of FluLaval seasonal influenza vaccine – October 5, 2006 – ID Biomedical Corporation, Quebec, Canada
- Approval of the first U.S. vaccine for humans against the avian influenza virus H5N1 – April 17, 2007 – sanofi pasteur, Swiftwater, PA
  - intended for immunizing people 18 through 64 years of age who could be at increased risk of exposure to the H5N1 influenza virus contained in the vaccine.
  - two intramuscular injections, given approximately one month apart.
  - purchased by the federal government for inclusion within the National Stockpile for distribution by public health officials if needed.

# Accomplishments (cont..)

- Issued “Draft Guidance for Industry: Characterization and Qualification Cell Substrates and Other Biological Starting Materials Used in the Production of Viral Vaccines for the Prevention and Treatment of Infectious Diseases,” September 28, 2006
- Issued Final Guidance for industry on clinical data needed to support licensure of pandemic and seasonal influenza vaccines – May 31, 2007



# Accomplishments (cont...)

- Continued work on CBER/WHO/Health Canada global regulatory collaboration on pandemic vaccines.
- Draft consensus documents were reviewed at a WHO-affiliated meeting hosted by FDA, in Bethesda, Maryland, in June 2006 and in Geneva, Switzerland in June 2007, hosted by WHO. A plan has been proposed to make a consensus document available later in 2007.

# Accomplishments (cont...)

- Continue conducting or participating in various meetings and workshops regarding current Good Manufacturing Practice (CGMP) for vaccines. These meetings began in August 2005 in the United States and Europe and continue.
  - Workshop August 28, 2007.
- Participated in Agency Pandemic GMP Workshop for foreign regulatory counterparts throughout the world – May 15-18, 2007

# **Pandemic Influenza: Meeting the Challenges**

- Build review and testing capacity – including for surge and new vaccine technologies (e.g., adjuvanted, recombinant, or cell-culture grown vaccines)**
- Influenza virus strain and reagent preparation needed for vaccine manufacture and testing**
- Improved assays for evaluating vaccine potency, immune responses, etc.**
- Support DHHS planning and vaccine development activities – enhance emergency vaccine availability preparedness**

# CBER Pandemic Flu Steering Committee

- Participants from all CBER offices
- Continuity of Operations
  - Essential functions
  - Essential personnel
- Work with FDA Pandemic Preparedness Task Force to address agency-wide issues

# FDA Pandemic Influenza Preparedness Strategic Plan

- Issued March 14, 2007
- Tied to National Strategy
- Defines FDA's Roles and Responsibilities
- Discusses FDA's Accomplishments to date
- Outlines FDA's Objectives, Actions and Deliverables

[http://www.fda.gov/oc/op/pandemic/strategicplan03\\_07.html](http://www.fda.gov/oc/op/pandemic/strategicplan03_07.html)

# We're Here to Help You!

[WWW.FDA.GOV/CBER](http://WWW.FDA.GOV/CBER)

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