CBER Update

12th Annual GMP by the Sea
August 27, 2007
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Office of Compliance and Biologics Quality

FDA

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

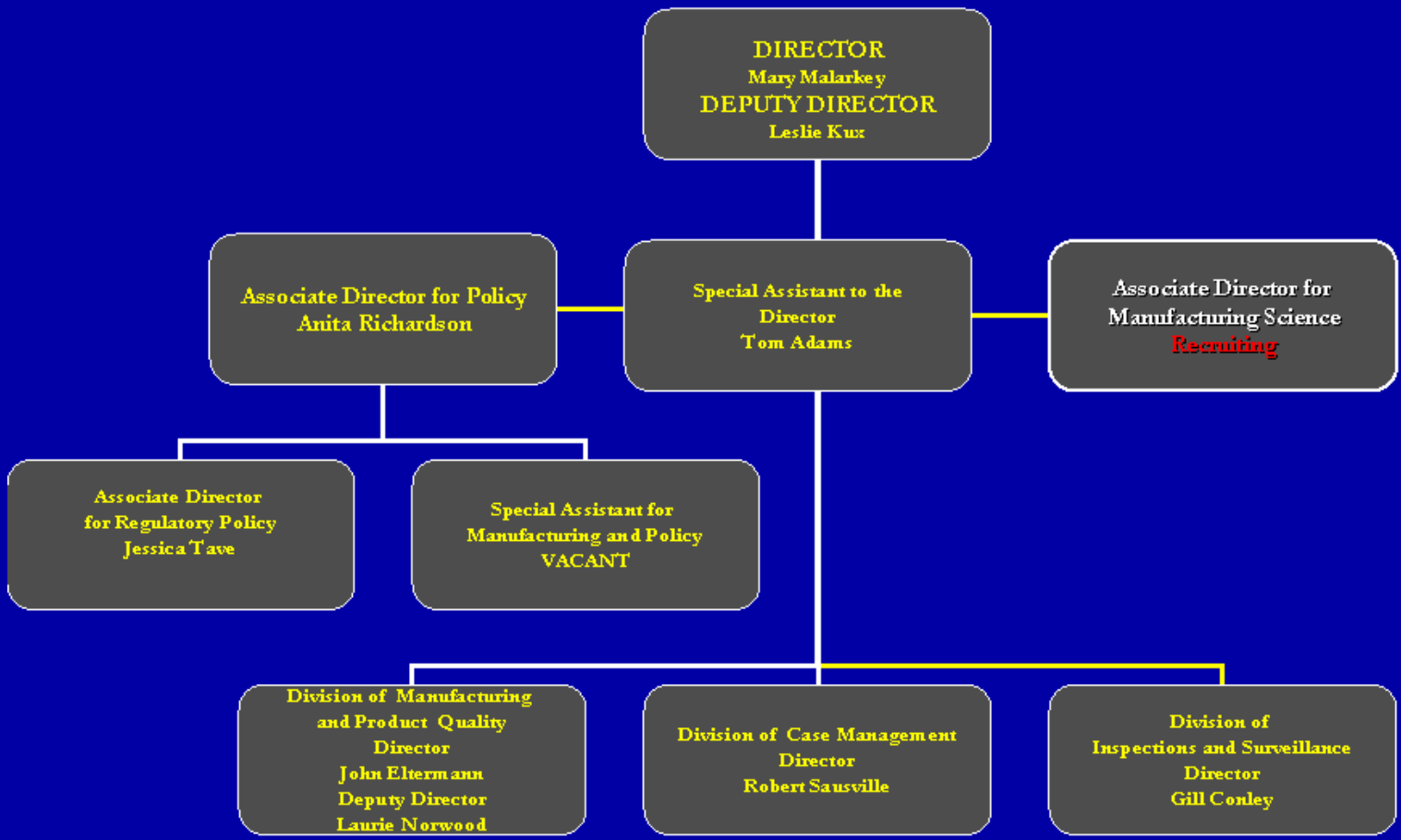
Manufacturing and Quality

- 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

Office of Compliance and Biologics Quality



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.)

"A stumble may prevent a fall."
— Thomas Fuller

The Numbers

FY06 - Recalls

Product	FY03	FY04	FY05	FY06
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
TOTAL	**1864**	**2058**	**2450**	**1841**

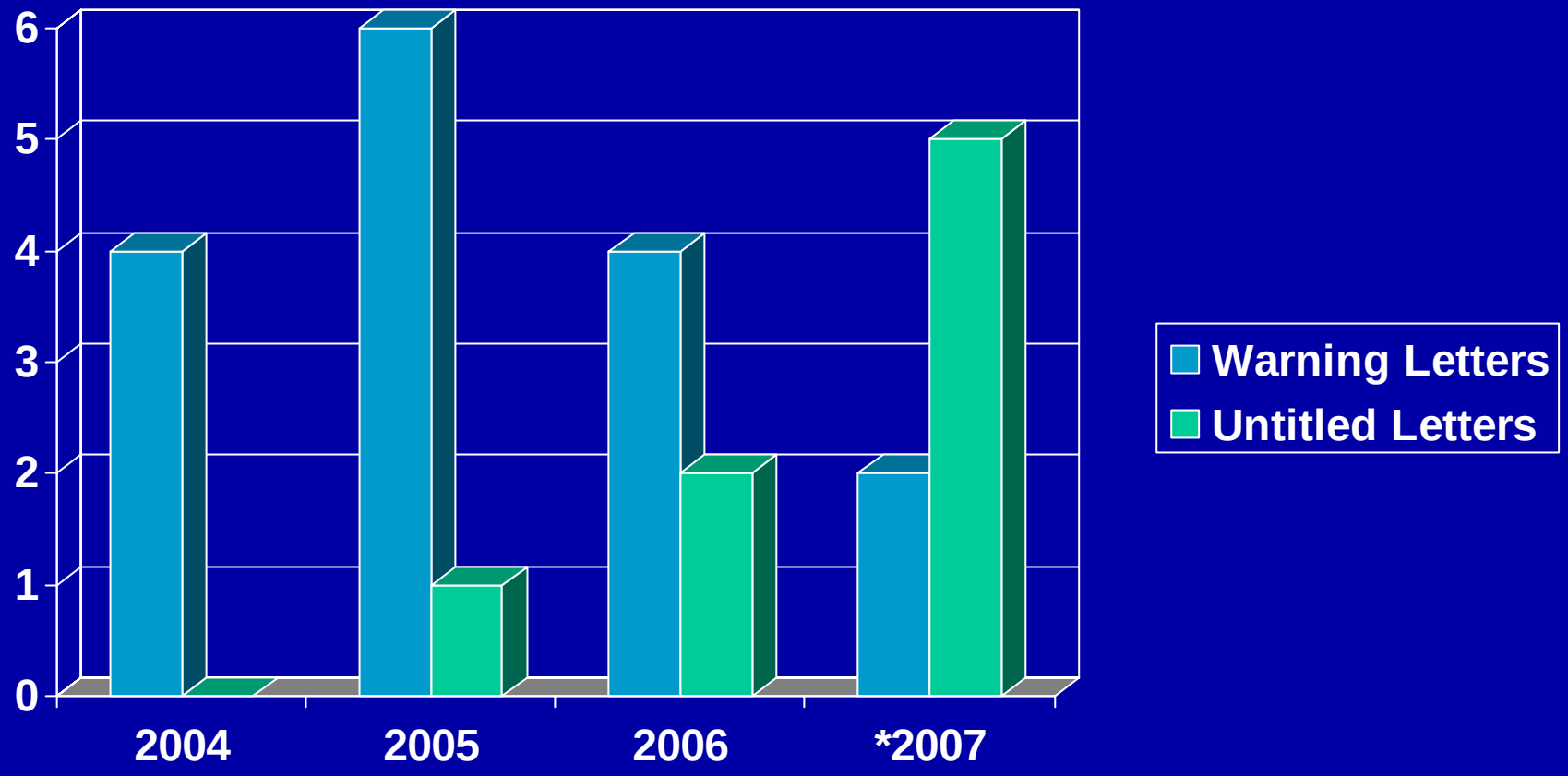
FY06 - Biological Product Deviation Reports – Drugs and Devices

	FY04		FY05		FY06	
Firm	#BPD	#eBPD	#BPD	#eBPD	#BPD	#eBPD
Allergenic	158	129	200	187	149	132
Plasma Derivative	44	22	47	14	35	18
Device	86	56	100	53	60	41
Vaccine	42	6	39	2	41	4
Total	**333**	**213**	**387**	**256**	**286**	**195**
		64.2%		66.5%		68.2%

FY06 - Biological Product Deviation Reports – Drugs and Devices

MANUFACTURING SYSTEMS	# OF REPORTS		
	FY04	FY05	FY06
Incoming Material Specifications	17	15	5
Process Controls	38	28	26
Testing	19	21	18
Labeling	37	73	33
Product Specifications	201	235	181
QC & Distribution	14	13	22
Miscellaneous	2	0	1

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 Evaluation

- Improve operations of Team Biologics through efforts of working groups for the following:
  - Implement Quality Management System
    - Implementation dependent on IT resources ☆
  - Create metrics and perform external impact evaluation ✔
  - Standardize training/qualifications for the Core Team members ✔

Team Biologics Evaluation

- Risk-based work planning ✔ ✯
- Increase communication between Headquarters and the field ✔
- Defines roles and responsibilities of the Biologic Products (Field) Committee and Team Biologics Operations Group ✔

Team Biologics Operations Group

- Implementation driven by Team Biologics Operations Group (CBER/CDER/ORA)
- QMS implementation
  - Quality Policy was developed
  - SOPs were revised in keeping with QMS provisions
  - Quality Assurance Programs were developed for inspection and compliance activities
- Working with the Pharmaceutical Inspectorate as a QMS is implemented

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

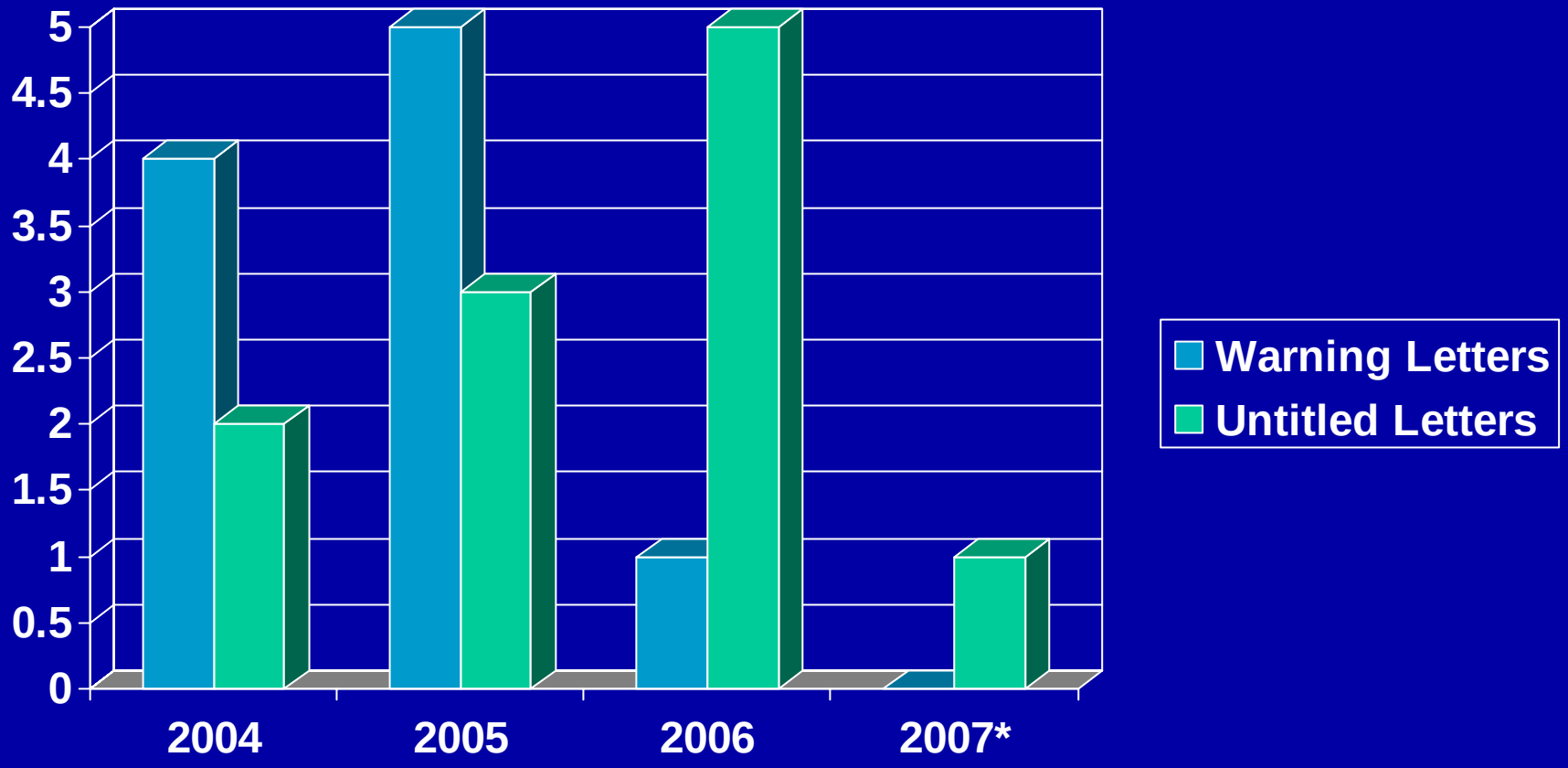
	FY04	FY05	FY06	FY07*
Clinical Investigators	4	12	0	3
Sponsors	0	2	1	1
Sponsor-Investigator	1	0	1	0
IRBs	0	0	3	2
GLP	0	0	0	2

As of July 31, 2007

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

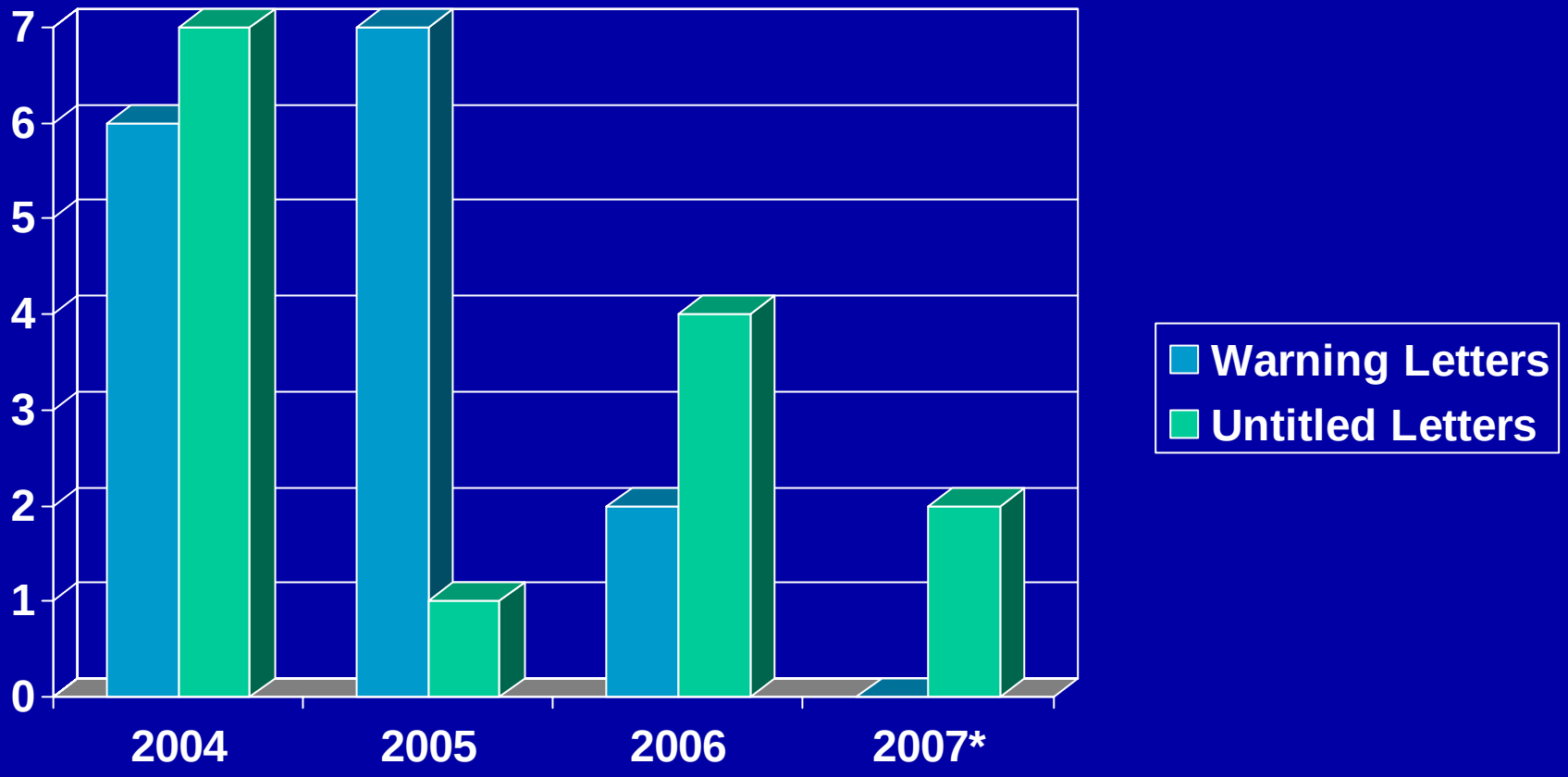


* As of July 31, 2007

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
- www.fda.gov/oc/buyonline/buyonlineform.htm

Advertising and Promotional Labeling

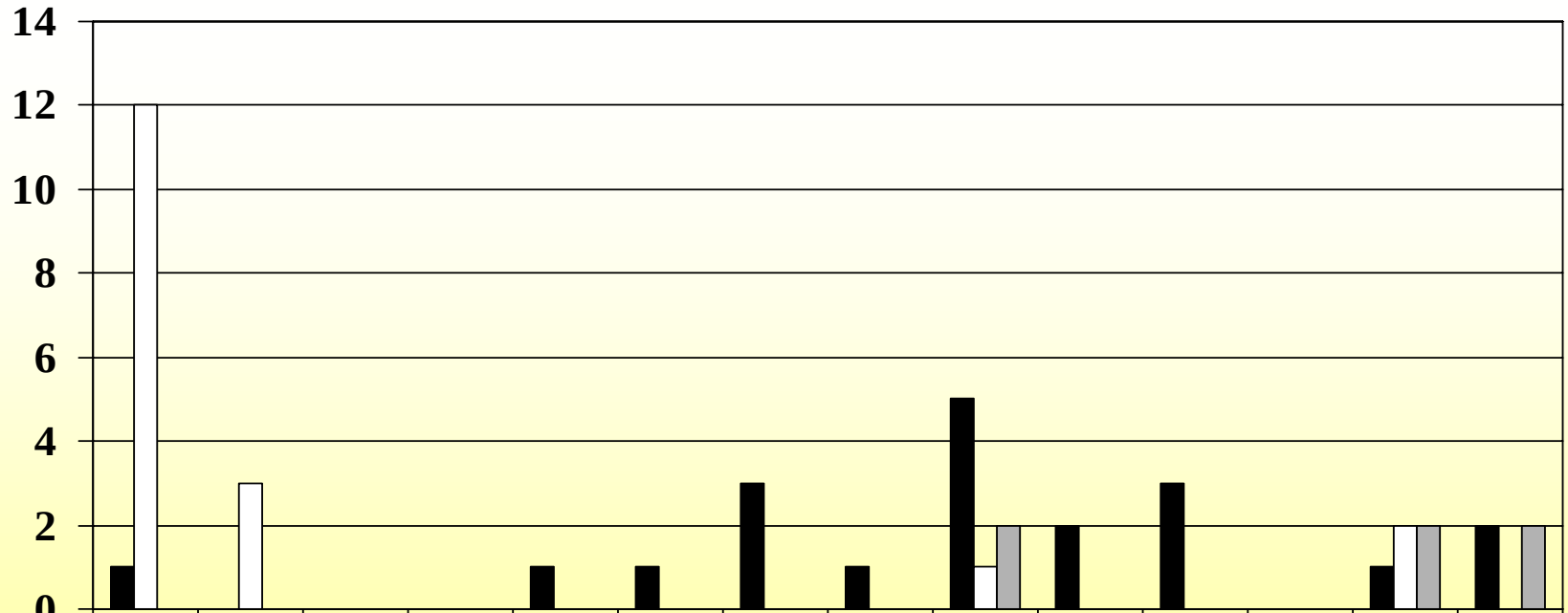


* As of July 31, 2007

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)]

Human Cells, Tissues and Cellular and Tissue Based Products



	FY94	FY95	FY96	FY97	FY98	FY99	FY00	FY01	FY02	FY03	FY04	FY05	FY06	FY07 *
WL's	1	0	0	0	1	1	3	1	5	2	3	0	1	2
Orders	12	3	0	0	0	0	0	0	1	0	0	0	2	0
Other*	0	0	0	0	0	0	0	0	2	0	0	0	2	2

* As of July 31, 2007

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

Areas Considered

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

Inspections

- 2023 registered establishments; 859 manufacture from non-living donors
- Focused inspections of 153 musculoskeletal recovery firms
- Assignment designed to enhance detection of violative practices that could result in use of ineligible donors
- Some deviations identified that require correction but no major inaccuracies or deficiencies in records that could put recipients at risk

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..)

- Sponsoring 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 have been invited 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

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

“I look to the future, because that is where I’m going to spend the rest of my life."

— George Burns

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**

We're Here to Help You!

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