FDA Compliance Update: Quality Systems

PDA/FDA Joint Meeting

September 10, 2008

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Office of Compliance and Biologics Quality

Summary

- CBER Priorities 2008
- Quality Systems
  - Internal
  - External
- Amendment to CGMP Regulations for Finished Pharmaceuticals – where are we?

2008 CBER Priorities

- **Pandemic/emerging threat preparedness**
- **Enhance product safety and confidence**
  - Interdisciplinary safety teams, FDAAA, new sources and approaches to data, better communication
- **Improve manufacturing and product quality**
  - **Risk based and preventive compliance, product testing, assay and standards development, CMC QS**

2008 CBER Priorities (cont..)

- **Innovative, safe, effective products to patients**
  - Critical Path, Tissue Engineering Team, Blood Cell Preservation, Genomics, Research Management
- **Strengthen human and organizational resources**
  - Succession planning, **continual process improvement system**, staff competencies &training
- **Global public health and globalization**
  - Products for public health needs, Global Vaccine Initiative, product and supply chain quality/availability, harmonization and collaboration

Knowledge, Risk, & Oversight

- **•Effective Understanding for Appropriate Regulation**
  - Increasing complexity results in increasing unknowns
  - Scientific foundation will need to be established and effectively communicated
  - Risk will have to be appropriately assessed, managed and communicated
  - Product Quality & Safety will need appropriate oversight

Lessons Learned

- Early and continued interactions with sponsors/ manufacturers and integration of review and CGMP issues has proven beneficial, particularly when **complex and/or innovative technologies** are proposed in facilitating product development, manufacturing and/or continual improvement

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.)

Internal Quality Systems: Examples

- **Division of Product Quality/OVRR**
  - Quality environment for critical product testing (lot release) and standards activities
  - Ongoing efforts toward ISO certification
- **Quality System for CMC Review**
- **Team Biologics QMS**
  - Quality Policy
  - Quality Assurance Programs developed and implemented for investigators and compliance officers (ORA and CBER)

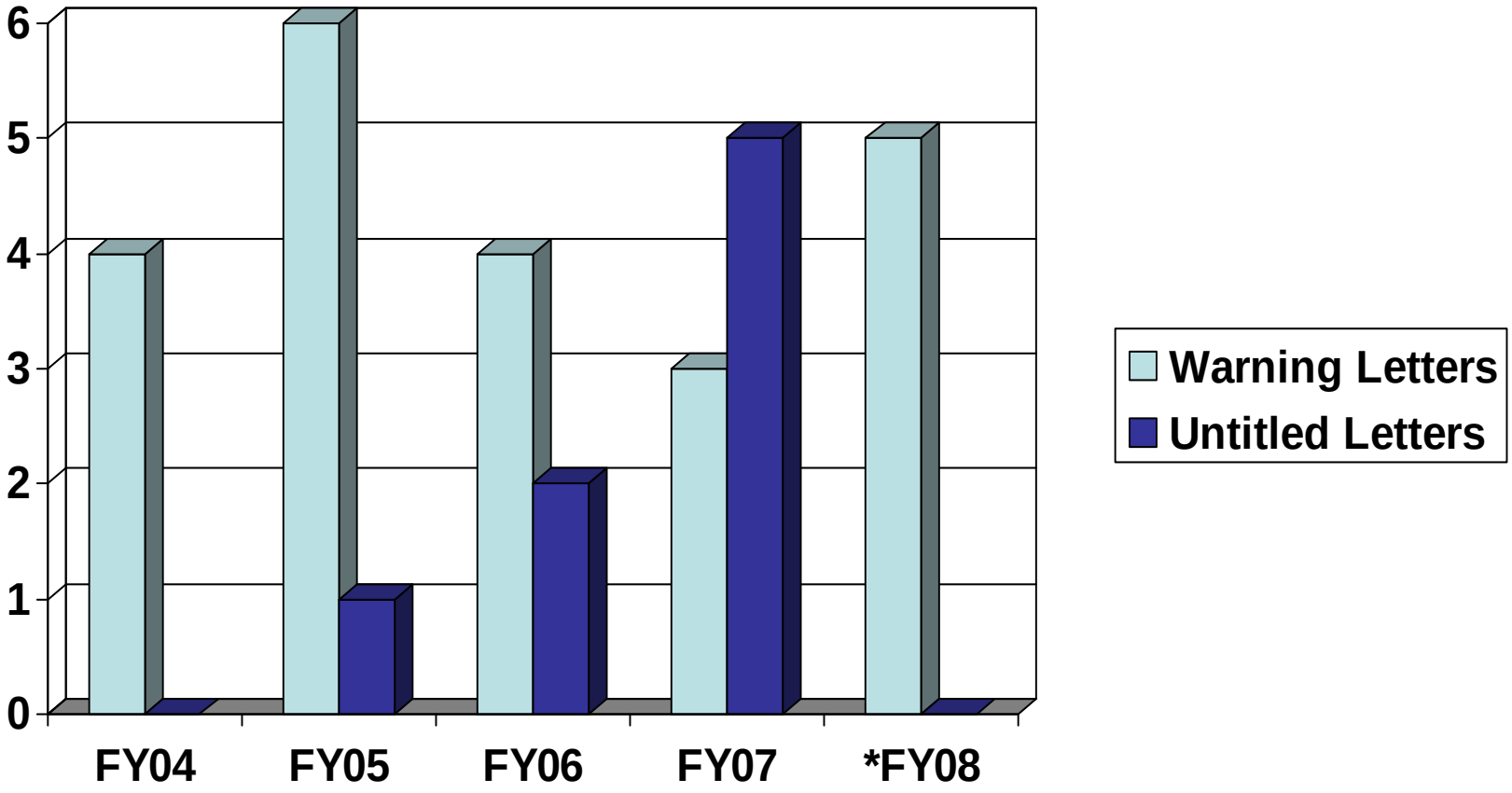
Internal Quality Systems: Risk Management - Examples

- Risk assessments have been submitted reviewed by CBER as part of applications and supplemental applications – DMPQ
  - Recommend contact review division if you wish to submit a risk assessment
- Use of risk-based inspection approaches – annual assessment
- Risk communication – there are risks in conveying uncertainties
  - Decreased use of safe products

External Quality Systems

- Continued outreach to industry on implementation of quality systems
- Problems still observed
  - Warning letter citations frequently directly involve the Quality Unit
- Progress has been made
  - Implementation of robust quality systems – often after compliance “problems”
- Desired state?
  - Proactive implementation before “problems” occur

Biological Drug and Device



*As of July 31, 2008

Top Five Citations – Biological Drugs

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

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

Drug Product CGMP Regulations

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

GMP Regulations Working Group: Results

- Final rule published on September 8, 2008 in the Federal Register, Volume 73, pages 51919-51933
- Effective date of the rule is December 8, 2008

GMP Regulations Working Group: Members

- Pat Alcock, ORA,ORO
- Diane Alexander, CBER, OCBQ
- William Bargo, CVM, OSC
- Dennis Bensley, CVM, ONADE
- Fred Blumenschein*, CDER, OC
- Walt Brown, ORA,OE
- Elizabeth Cormier, CVM, ONADE
- Mary Davis-Lopez, CBER, OCBQ
- Kevin Fain, OC, OCC
- Jo Gulley, CVM, OSC
- Chris Joneckis, CBER, OD
- Joan Loreng, ORA, ORO
- Sharon Mayl, OC, OPPL
- Grace McNally, CDER, OC
- Rosa Motta, CDER, OC
- James Nitao, CVM, ONADE
- Charles O'Brien, CVM, ONADE
- LuAnn Pallas, ORA,OE
- Brian Pendleton, CDER, ORP
- Michael Rogers, ORA,ORO
- Jessica Tave, CBER, OCBQ
- PM – Vikki Kinsey, CDER, OEP
- Co-chairs
  - Brian Hasselbalch, CDER, OC
  - Mary Malarkey, CBER, OCBQ

*Former Co-chair, retired

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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