Center for Drug Evaluation and Research: Biotechnology Products and Agency Initiatives

WCBP 1/12/2009

Steven Kozlowski, Director
Office of Biotechnology Products
OPS, CDER, FDA
The Year of Living Gloomily
By Eric Wiener

WARNING: [If you read about the economy] Dizziness and pangs of existential angst may result… If you are near retirement age… consult a physician before reading.
1902 Biologics Control Act

• The "Virus-Toxin Law,“
  – Regulatory authority over the processes used to make biological products, or biologics
  – Responsibility to ensure their safety

• Drivers for Law
  – A horse named Jim whose tetanus-contaminated serum was used to produce a diphtheria antitoxin that caused the deaths of thirteen children in St. Louis, Missouri.
  – Contaminated smallpox vaccine which killed nine children in Camden, New Jersey.
1938 Federal Food Drug & Cosmetic Act

- New Drug Application (NDA)
  - Drug composition, manufacturing & quality
  - Report on safety

- Driver of Law
  - In 1937, S. E. Massengill Co., a pharmaceutical manufacturer, created a preparation of sulfanilamide using diethylene glycol (DEG) as a solvent, and called the preparation "Elixir Sulfanilamide"
  - More than 100 deaths
  - Under Pure Food & Drug Act of 1906
    - Just misbranded “Elixir”
Pharmaceutical Quality for the 21st Century

• In 2002, FDA identified a series of ongoing problems in pharmaceutical manufacturing
  – High costs cGMP/regulatory compliance
  – Poor encouragement of innovation & efficiency
  – Lack of agility
    • long cycle times
    • challenges for scale-ups/new production sites

• The Desired State: A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drug products without extensive regulatory oversight
  • Janet Woodcock
Quality Initiatives

• CGMP for the 21st Century
  – risk-based (ICH Q9)
  – Quality Systems (ICH Q10)

• Quality by Design (QbD):
  – A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management (ICH Q8R1)

• Process Analytical Technology
  – material attributes
  – on or at line measurements
  – impact process parameters
Potential Benefits for Embracing the New Paradigms

- Smoother transitions from IND to Licensure
- Increase productively/efficiency
- Less lot rejections, recalls, and investigations for manufacturing deviations
- Expedited implementation of process changes
- Manufacturing processes that are adaptable
- **Reliable supply of high quality products**
  - Fewer inspections
  - Fewer submissions to the Agency
Outline

• QbD for Biotech Products
• Safety & Rare Events
• Rare Events & Quality
• Research & Critical Path
• Challenges & Future
The product is the process...a biologics mantra

Manufacturing Process

Variability

Raw Material → Manufacturing Process → Product

Input Response

Measurement Dependant Process Variables

Endpoint Response

Jon Clark
Risk Assessment to DOE

- Assign relative risk for each factor
  = [severity]
  x [occurrence]
  x [detectability]

Risk assessment includes process develop., manufact., QC staff, etc.

- Screening DOE
- Optimization

FMEA

Severity

Occurrence

Surface Response Plot
Design Space Lifecycle

Overlay Lab
Scale Response Surfaces to form an Initial Design Space

• Managing uncertainty
  – Lack of 1st Prin. Models
  – Complex products
  – Complex processes

• Multivariate SPC
  – Facilitates moving across scales

Adapted from T. Kourti
From Attributes to Spaces

Critical Quality Attribute (CQA): A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality [Q8R1]
Is Oxidation Without Impact on Activity?

Is Level Low Enough not to Matter?

Detectability of Oxidation with Impact?

Acceptable Product

Batch Failure

Clinical Failure

Functional Event Sequence Diagram
### Assigning Probabilities

- **Related Product or Component**
  - Direct Data (clinical)
  - Models (animals, bioassays)
- **Same Product**
  - Models (animals, bioassays)

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Moving Forward

- Knowledge in submissions
  - Data needed to support knowledge
- Platform Strategies
- Link to small-molecule learnings
  - ONDQA pilot; PMP
- Mock Case Studies
  - ISPE PQLI, EFPIA
  - Conformia
    - Novel approach to CQAs
    - Future workshops
OBP Pilot Program

FR Notice July 2, 2008

- To define clinically relevant attributes for protein products (regulated by OBP) and link them to manufacturing processes
- To consider quality-by-design (QbD) approaches to unit operations in supplements (10) as well as original applications (5)
- To explore the use of protocols submitted under (21 CF 314.70(e) and 601.12(e))
- One application accepted (full BLA)
- Three more under consideration
- Applications close 9/30/2009
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2007 FDAAA

• Postmarket safety surveillance
  – Section 905 of FDAAA calls for the HHS Secretary to develop methods to obtain access to disparate data sources and to establish a postmarket risk identification and analysis system

• Access to data from
  – 25 million patients by 7/1/2010
  – 100 million patients by 7/1/2012
Sentinel Initiative

- Sentinel System—a national, integrated, electronic system for monitoring medical product safety
- **Active Surveillance**
  - Linking, in a secure fashion, existing electronic databases run by private health plans, insurance plans, government agencies, industry
  - Querying electronic health records, claims databases, etc. to pick up early warnings of adverse events
  - Studying de-identified data on millions of people in something much closer to real time

The Sentinel Initiative…May 2008 Report
Office of Critical Path Programs www.fda.gov/oc/initiatives/criticalpath/
Sentinel

Research Component

Data (Remain with data owners)

Sentinel System Architecture

- Database
- Database
- Database
- Database

Sentinel Initiative
Private-Public Partnership
- FDA
- Partners (e.g., data owners)
- Subject matter experts
- Other government agencies

Query Databases
- Data owner consent
- Established privacy security

Link Safety to Quality
Outline

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Heparin Adverse Event Review

FDA Website: http://www.fda.gov/cder/drug/infopage/heparin/default.htm
Overview & 2/11/08 Public Health Advisory

- The serious adverse events include:
  - allergic or hypersensitivity-type reactions
  - nausea
  - vomiting
  - sweating
  - shortness of breath
  - severe hypotension requiring treatment.

Baxter Press Release
1:10,000

• High doses (5000-50,000 units) given bolus
• Most events developed within minutes
Oversulfated chondroitin sulfate is a contaminant in heparin.

Oversulfated chondroitin sulfate has partial activity in USP bioassay for heparin.
Heparin was a Wakeup Call

• Up to 30% contamination of finished product
• Present worldwide in various APIs: many countries affected
• Undetected by acceptance and release testing
• Persisted in drug supply until serious adverse events triggered investigation
• Analytical methods were critical in identifying and resolving the problem (CE and H-NMR)
Heparin Lessons

• Initial focus was on inspectional issues
  – vigilance throughout supply chain

• CE is a routine assay for current complex product
  – would have picked up contaminant in crude, API or finished product

Update Analytical Methods

Sub micron particulates

Regulatory agencies should have a transparent approach to newly discovered pre-existing variability

Contaminated heparin associated with adverse clinical events and activation of the contact system.

Outbreak of adverse reactions associated with contaminated heparin.

Linkage of Quality to Safety
Outline

• QbD for Biotech Products
• Safety & Rare Events
• Rare Events & Quality
• **Research & Critical Path**
• Challenges & Future
OBP Research Areas

- Protein structure/function
- Bioassays
- Immunogenicity
- Adventitious Agents
- Biotechnology manufacturing science
- Cutting edge protein characterization
  - Higher order structure
  - Post translational modifications
- Protein device interactions
- Protein environmental interactions
Critical Path Projects

• Development of PAT tools for automated sampling and analysis of mammalian cell culture
  – Kurt Brorson & Jun Park

• Multiple Projects on Cancer Biomarkers
  – Wen Jin Wu
  – Baolin Zhang

• Assay for early indicators of innate immune activation & inflammation in non-human primates
  – Daniela Verthelyi

• Cytokine Therapeutics Workshop with NYAS
  – Amy Rosenberg & Ray Donnelly
Identifying indicators of cardiac toxicity

- FDA and Mortara Instruments are working to create a repository for digital ECGs and review tools.
- Currently, the warehouse contains more than one million ECGs

Advancing biomarker qualification

- The Predictive Safety Testing Consortium has the CPath Institute, 17 companies and the FDA as partners
- A set of nephrotoxicity biomarkers were submitted to FDA for qualification in 2007
Big Critical Path

- Large programs for drug-induced liver injury (DILI) & EKG changes (e.g. QT intervals)
  - Generally small-molecule toxicities
- Consider large programs for Biologics
  - Immunogenicity
  - Adventitious agents
- Large programs involve consortiums that include government, industry, academia & other stakeholders
  - Complex agreements
  - Need to agree on intellectual property, share benefits & credit
  - Predictive Safety Testing Consortium
    - Meetings with more lawyers than scientists
Outline

• QbD for Biotech Products
• Safety & Rare Events
• Rare Events & Quality
• Critical Path Research
• Challenges & Future
Trends in Product Submissions

- **Total NMEs Rec'd by FDA**
- **Original BLAs**

NMEs & BLA Received by FDA 1997-2003
Critical Path March 2004

- mAb Related New Product INDs

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• Recombinant Proteins
  – Cytokines, Toxins, Receptor Ligands
• Quality by Design Pilot program
• New Reviewer hires & training program
• Enzymes
  – Science driven ERT comparability evaluation
  – Advisory committee meeting on PEP viral risks
• Immunogenicity Consults
• Review of data supporting delivery of an antibody to the Strategic National Stockpile
• Future Challenges
  – *Follow on proteins*
  – Novel adaptive protein scaffolds
• Conjugates
• Combination Products
  – Proteins in devices
Matching Engineering to Knowledge
Future Directions

• Quality by Design Manufacturing
• Science & Risk-based linkages of Q, S & E
  – Capture quality in passive & active surveillance
  – Apply science to understand the impact of quality
• Science based updating of analytics
  – Regulatory approaches to facilitate
• Big Critical Path Projects for Biologics
• More complex product engineering to improve efficacy or deal with complex diseases
  – Better regulatory approaches to fixed combination therapies & combination products
Credits

- Barry Cherney
- Patrick Swann
- Emily Shacter
- Keith Webber
- Susan Kirshner
- Janet Woodcock
- Moheb Nasr
- Ali Al-Hakim
- Jon Clark
- Christine Moore