FDA Perspective: Recent Trends in the Regulation of Biopharmaceuticals

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Sarah Kennett, Ph.D.
Division of Monoclonal Antibodies
Office of Biotechnology Products
OPS, CDER, FDA
Outline

• Trends in mAb Development
• FDA Quality Initiatives
  – Pharmaceutical Quality (21st Century)
  – Reorganization of OPS
  – Quality by Design in OBP
• Post-Approval Changes
• Process Validation
• Breakthrough Designation/Accelerated Development Programs
• Biosimilars
• Recently Published Guidance Documents
Monoclonal Antibody Development Trends
History of Monoclonal Antibodies

- **1986**: Orthoclone
  - 1st mAb
- **1992**: DMA founded
- **1994**: ReoPro
- **1997**: Rituxan, Zenapax
- **1998**: Zenapax
- **1998**: Enbrel
- **1998**: Mylotarg, Humira
- **2000**: Zevalin
- **2000**: Vectibix
- **2002**: Mylotarg, Humira
- **2006**: Vectibix
- **2008**: Cimzia
- **2011**: Adcetris
- **2012**: Gazyva
- **2013**: raxibacumab
- **2014**: 43 mAbs
  - 7 Fc-fusion

- **1986**: Murine
- **1994**: Chimeric fragment
- **1997**: Intact chimeric humanized
- **1998**: Fc-fusion
- **2000**: mAb-drug Conjugate NDA
- **2002**: Therapeutic radioimmunoconjugate
- **2006**: Human/mouse
- **2008**: Pegylated
- **2011**: mAb-drug Conjugate BLA
- **2012**: QbD/design space
- **2013**: Animal rule

M. Shapiro, 2013
mAb Development in the 21st Century

- Fc engineering to reduce or enhance effector function
  - Specific mutations
  - CH domain combinations
  - Glycoengineering
- V region engineering to enhance PK
- mAb fragments
  - sFv and variations
  - Single domain mAbs and variations
- Novel mAb Constructs (with or without Fc region)
  - Bispecific (engineered to ensure inclusion of both “arms”)
  - Multispecific constructs
  - Fc constructs
- Conjugates
  - Increasing number of ADC submissions
  - Novel types of conjugates (cytokines, enzymes, toxins, peptides, imaging agents, etc.)
- Cocktails (2 – 26)
Update on Quality Initiatives
Pharmaceutical Quality

- Dr. Janet Woodcock, defined high quality drug products as those that,
  - 1) consistently and reliably deliver the clinical performance and other characteristics stated on the label,
  - 2) are free from contamination, and
  - 3) are available.

Retrospective Quality

• 1902 Biologics Control Act: "Virus-Toxin Law,"
  • Regulatory authority over the processes used to make biological products, or biologics
  • Responsibility to ensure their safety
  – Tetanus-contaminated diphtheria toxin antiserum that caused the deaths of thirteen children; Contaminated smallpox vaccine

• 1938 Federal Food Drug & Cosmetic Act
  • New Drug Application (NDA)
  • Drug composition, manufacturing & quality
  • Report on safety
  – Sulfanilamide “elixir” using diethylene glycol (DEG) as a solvent caused more than a 100 deaths
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
Prospective Quality Initiatives

- CGMP for the 21st Century
  - Risk-based (ICH Q9)
  - Quality systems (ICH Q10)
  - Linking material attributes and process parameters to DS CQAs (ICH Q11)

- Process Analytical Technology
  - material attributes
  - on or at line measurements
  - impact process parameters

- 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 Q8R2)
FDA/CDER Review in the 21st Century

- 21st Century Review
- PDUFA V

  - Describes the PDUFA V review model
  - Useful tool for understanding our internal deadlines

CDER Office of Pharmaceutical Quality (OPQ)

- Combines components of current CDER Office of Pharmaceutical Sciences (Office of Biotechnology Products will remain -in a modified format), CDER Office of Generic Drugs, and CDER Office of Compliance
  - To help deal with increasing product complexity and global challenges
- Intended to provide better alignment among all quality functions (review, inspection, research)
- Focus areas for new office:
  - Patient-centric approach to the assessment of quality
  - Integrated approaches for review and inspection
  - Risk-based approaches to review and inspection
  - Efficiency and risk-based work prioritization
  - Modern regulatory science approaches (e.g., clinically relevant specifications, statistical sampling)
Aggregates and Particulates: Patient Safety Concerns – Relationship to Testing and Manufacturing Process

• Product Related Aggregates
  – Relationship with immunogenicity demonstrated for larger aggregates
  – Unknown relationship to smaller subvisible particles (2-10 μm) and aggregates
  – Continuing development
    • New orthogonal methods to characterize particles
    • Expectation for characterization and consideration of smaller particles during comparability studies (for example)

• Container Closure and Fill Line Related Particles
• Visible particulates – USP <790> (August 2014)
Quality by Design:  
Office of Biotechnology QbD Pilot (OBP) Program

– Purpose
  • To define clinically relevant attributes for protein products and link them to manufacturing processes
  • To consider QbD approaches to unit operations in supplements and original applications
  • To explore the use of protocols submitted under QbD submissions

– Progress
  • Program closed to new applicants, reviews ongoing
  • 6 BLAs accepted (5 MAbs, 1 fusion protein)
  • 4 Supplements (2 MAbs, 1 therapeutic protein, 1 multiproduct)
  • 25 Meetings have been held
  • One application followed the same pathway as the small molecule EMA-FDA pilot for QbD
OBP QbD Biotech Approvals

• One manufacturing supplement with an expanded change protocol covering multiple products and manufacturing sites.
  – Evaluation of this supplement involved effective interactions between review and compliance functions at CDER.
    • MAPP 4730.3 OBP & DMPQ Interactions on BLAs

• One pilot BLA approved, but design space not accepted
  – Issues with CQAs, scaled down models & other manufacturing problems

• One BLA approved with a design space
  – Not in pilot
Critical Thinking

• Critical quality attribute identification challenges
  - many different risk ranking strategies
    ➢ detectability is not part of this assessment
  - acceptance criteria
  - levels near or below the limit of detection
  - appropriate consideration of contribution to safety, efficacy, PK, immunogenicity

• Critical process parameter identification challenges
  - ranges to study
  - validity of small scale models (use of offsets)

• Criticality is a continuum not a step function
  - regulatory commitments part of overall Control Strategy- not all “in” or “out” based on “green” or “red” criticality
Looking Ahead

- Receiving non-pilot applications and meeting packages with advanced science and risk approaches
- QbD is a continuum not a step function
  - Many traditional pharmaceutical development approaches are consistent with QbD; all applications have some aspects of science and risk based approaches
- CDER is moving away from designating applications as “QbD” or “non-QbD”
- The level and nature of enhanced product and process knowledge determines...
  - regulatory flexibility
    - Design space
    - Regulatory plan
Post Approval Changes
Trends in Post-Approval CMC Changes

Traditional BLAs

- Process improvements
  - Yield, safety
- Facility design
  - Single use equipment, modular design
- Larger changes
- Appropriate comparability protocol/studies
- Introduction of new analytical methods for “old” products

QbD approach

- More use of expanded change protocols
- Challenges to transfer design space to different facilities
  - Can some small scale studies, DOE apply to new site?
  - Different design space for different sites?
Process Validation

- Product lifecycle concept
- FDA guidance in alignment with ICH Q8, Q9, Q10
- Encourage use of modern pharmaceutical development concepts, quality risk management, quality systems
- Process validation is “the collection and evaluation of data, from the process design stage through commercial production.”
  - Process Design, Process Qualification, Continued Process Verification
- Need to understand and control variation
- Process Performance Qualification
  - “combines the actual facility, utilities, equipment, and the trained personnel with the commercial manufacturing process, control procedures, and components to product commercial batches.”
  - “confirm the process design and demonstrate that the commercial manufacturing process performs as expected”
- “FDA expects that concurrent release [of PPQ batches] will be used rarely.”
- “For biotechnological processes, or for aseptic processing and sterilization process steps for drug substances, the data provided in support of process validation is included as part of the marketing application.” [ICH Q11]
Breakthrough Therapy Designation
Expedited Development
To address unmet medical need in the treatment of serious or life-threatening conditions

- Fast Track Designation
  - Actions to expedite development and review: frequent interactions
  - Rolling review, may be eligible for priority review
- Accelerated Approval
  - Use of a surrogate endpoint/intermediate clinical endpoint
- Priority Review Designation
  - 6/8 month BLA review clock (vs. 10/12 month standard)
- Breakthrough Therapy Designation

“The sponsor of a product that receives an expedited drug development designation will probably need to pursue a more rapid manufacturing development program to accommodate the accelerated pace of the clinical program. The sponsor’s product quality team and CMC teams should initiate early communication with FDA to ensure that the manufacturing development programs and timing of submissions meet the Agency’s expectations for licensure or marketing approval.”
Breakthrough Therapies

• BT designation is intended to expedite the development and review of drugs for serious or life-threatening conditions. The criteria for breakthrough therapy designation require preliminary clinical evidence that demonstrates the drug may have substantial improvement on at least one clinically significant endpoint over available therapy.

• CDER Actions (through 4/18/14)
  – FY 2012: 2 requests, 1 granted, 1 denied (CBER 0)
  – FY 2013: 92 requests, 31 granted, 52 denied (CBER 11/1, 10)
  – FY 2014: 56 requests, 10 granted, 19 denied (CBER 19/3, 13)
  – CY 2013: 3 approvals (obinutuzumab 11/1; ibrutinib 11/13)
  – CY 2014: 3 approvals
BT Designation Actions

• Meetings throughout the development of the drug

• Providing timely advice and interactive communication with the sponsor

• Taking steps to ensure that the design of the clinical trials is as efficient as practicable, when scientifically appropriate, such as by minimizing the number of patients exposed to a potentially less efficacious treatment

• Assigning a cross-disciplinary project lead for the FDA review team to facilitate an efficient review and to serve as a scientific liaison between the cross-discipline members of the review team (i.e., clinical, pharmacology-toxicology, chemistry, manufacturing and control (CMC), compliance)

• Involving senior managers and experienced review staff
CMC Development Considerations for BT Products

- Can process development keep pace with clinical development?
- Will the commercial manufacturing process be ready?
  - consistently and reliably deliver the clinical performance and other characteristics stated on the label
- Will it be sufficient to meet market demand?
- Can QbD approach and more rapid development for commercialization be implemented simultaneously?
- Sponsors should request CMC-specific meetings as soon as possible upon receiving BT designation.
Update on the Biosimilar Program
Biosimilar Workload Update

• CDER continues to meet with sponsors interested in developing biosimilar products.

• As of March 31, 2014, CDER had received 64 requests for an initial meeting to discuss biosimilar development programs for 13 different reference products and held 55 initial meetings with sponsors.

• CDER has received 22 INDs for biosimilar development programs, and additional development programs are proceeding under a pre-IND.
Shift in Workload

• CDER is actively engaging with sponsors, including holding development-phase meetings and providing written advice, for ongoing development programs for proposed biosimilar products.

• Most meetings currently being held are Biosimilar Product Development (BPD) meetings
  – 42 products are in the BPD Program as of March 31, 2014
  – Biosimilar sponsors are
    • Taking advantage of the BPD meetings
    • Engaging in the intended iterative process
New Guidance Documents
Select 2013-2014 Documents

• Draft Guidance: Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants (3/29/13)

To compliment 2012 Draft Guidances

• Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product
• Scientific Considerations in Demonstrating Biosimilarity to a Reference Product
• Guidance for Industry on Biosimilars: Q &As Regarding Implementation of the BPCI Act of 2009

• Draft Guidance: Expedited Programs for Serious Conditions – Drugs and Biologics (6/25/13)
Select 2013-2014 Documents

- Draft Guidance: Immunogenicity Assessment for Therapeutic Protein Products (2/8/13)
- Draft Guidance: Contract Manufacturing Arrangements for Drugs: Quality Agreements (5/24/13)
- Draft Guidance: Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products (6/6/13)
- Draft Guidance: Analytical Procedures and Methods Validation for Drugs and Biologics (2/19/14)
- CMC Postapproval Manufacturing Changes to be Documented in an Annual Report (3/4/14) Note: This applies to NDA/ANDA products
- Draft Guidance: Allowable Excess Volume and labeled Vial Fill Size in Injectable Drug and Biological Products (3/13/14)
- Interpreting Sameness of Monoclonal Antibody Products under the Orphan Drug Regulations (4/22/14)
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sarah.kennett@fda.hhs.gov