FDA Perspective: Recent Trends in the Regulation of Biopharmaceuticals

CMC Strategy Forum LATAM 2014

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Outline

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

mAb-doxorubicin (hydrazone)
History of Monoclonal Antibodies

DMA (Division of Monoclonal Antibodies)
founded 1992

Orthoclone 1st mAb

ReoPro

Rituxan Zenapax

Enbrel

Mylotarg

Humira

Zevalin

Vectibix

Cimzia

Adcetris

Gazyva


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 Glycoengineered QbD/design space

2013 Animal rule

2014 44 mAbs 7 Fc-fusion
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 (PAT)
  – 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 (Prescription Drug User Fee Act)

• CDER 21st Century Review Process Desk Reference Guide (NDA/BLA review process) with PDUFA V requirements incorporated
  – 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)
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
Lessons Learned

• 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?
Post Approval Change Submissions

2014 Guidance Document
• CMC Postapproval Manufacturing Changes to be Documented in an Annual Report (3/4/14)
• Applies to NDA/ANDA products only

1997 Guidance Document
• Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products
• Still in use for BLA products
Guidance for Industry
Analytical Procedures and
Methods Validation for Drugs
and Biologics

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication to the Division of Generic Drugs (HFA-360), Food and Drug Administration, 5600 Fisher Lane, Rockville, MD 20857. All comments should be identified with the docket number listed in the notice of availability for this document.

For questions regarding this draft document contact: (CDER) Leonard Boland, (CDER) Office of Communication, Outreach and Development at 301-443-8789 or 301-443-1081.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
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ICH HARMONISED TRIPARTITE GUIDELINE

VALIDATION OF ANALYTICAL PROCEDURES:
TEXT AND METHODOLOGY
Q2(R1)

Current Step 4 version
Parent Guideline dated 27 October 1994
Complementary Guideline on Methodology dated 6 November 1996
(incorporated in November 2005)

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

Method Validation and Transfer

2005

2014 draft
Method Validation

• FDA Guidance intended to compliment ICH Q2(R1)

• BLA submissions should include:
  – A full description of analytical procedures
  – Data to establish that the methods “meet proper standards of accuracy and reliability and are suitable for their intended purpose”

• Validation should be performed under an approved protocol following cGMP and should include predetermined acceptance criteria

• Validation typically includes:
  – Specificity
  – Linearity
  – Accuracy
  – Precision (repeatability, intermediate precision, and reproducibility)
  – Range
  – Quantitation limit
  – Detection limit
  – Robustness (data can also come from development studies)

• Compendial methods should be verified for suitability
Method Validation

• Lifecycle Management
  – Trend analysis
  – Appropriateness of method and new technologies should be evaluated over lifecycle
  – Samples should be archived

• Analytical Method Comparability Studies
  – New method equal or superior to original method
  – New method is not more susceptible to matrix effects
  – Stability indicating properties should be evaluated

• Analytical Method Transfer Studies
  – Two (or more) laboratories participate in the transfer protocol
  – A sufficient number of representative samples should be used (including forced degradation samples or samples containing product-related impurities where appropriate)
  – Accuracy and precision should be evaluated
  – Also see USP<1224> Transfer of Analytical Procedures
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 7/11/14)
  – FY 2012: 2 requests, 1 granted, 1 denied (CBER 0)
  – FY 2013: 92 requests, 31 granted, 52 denied (CBER 11/1, 10)
  – FY 2014: 76 requests, 20 granted, 35 denied (CBER 20/3, 16)
  – 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 May 31, 2014, CDER had received 67 requests for an initial meeting to discuss biosimilar development programs for 14 different reference products and held 57 initial meetings with sponsors.

• As of July 22, 2014, CDER has received 24 INDs for biosimilar development programs, and numerous 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
  – 43 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
Biosimilars Draft Guidance Documents

• Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants
• 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

FDA is currently reviewing and considering all comments received from the public hearing docket and those from the draft guidance dockets as we move forward to
  – Finalize the four draft guidances
  – Determine plans for developing future policies on biosimilars
Biosimilars Guidance Documents

FDA has identified additional guidances that they plan to publish in CY 2014:

• Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009

• Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product (published May 2014)

• Considerations in Demonstrating Interchangeability to a Reference Product

• Labeling for Biosimilar Biological Products

• Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act
New Guidance Documents
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: Expedited Programs for Serious Conditions – Drugs and Biologics (6/25/13)
- Draft Guidance: Analytical Procedures and Methods Validation for Drugs and Biologics (2/19/14)
- 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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Thank you for your attention

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