FDA Perspective: Recent Trends in the Regulation of Biopharmaceuticals

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Disclaimer

I represent the Office of Biotechnology Products in the Center for Drug Evaluation and Research. The topics discussed in my presentation reflect the current thinking within OBP/CDER, which has regulatory responsibility for most therapeutic proteins.

The Center for Biologics Evaluation and Research has regulatory responsibility for vaccines, blood and blood products and cell, gene and tissue therapies.
Outline

- Office of Pharmaceutical Quality
- Biosimilars
- Antibody Development and Engineering Trends
- Accelerated Developing Programs
- Lifecycle Approach to Process Validation
FDA’s Pharmaceutical Quality for 21st Century Initiative

Desired State

“A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high quality drugs without extensive regulatory oversight.”

- Dr. Janet Woodcock
Some Current Challenges

- Drug shortages
- State of quality (?)
- Knowledge and lifecycle management
- Internal process improvements needed
- Multiple systems and databases
- Need for risk based quality assessment
- Communication/silos
Office of Pharmaceutical Quality (OPQ)

Mission
The Office of Pharmaceutical Quality assures that quality medicines are available to the American public.

Vision
The Office of Pharmaceutical Quality will be a global benchmark for regulation of pharmaceutical quality.
Office of Pharmaceutical Quality (OPQ) – Effective as of January 11, 2015

• Combines components of current CDER Office of Pharmaceutical Sciences and CDER Office of Compliance
  – To help deal with increasing product complexity and global challenges
• Intended to provide better alignment between 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)
OPQ Mission / Goals / Objectives

• Creates ‘One Quality Voice’ by integrating review, quality evaluation, and inspection across the product lifecycle
• Balances potential quality risks with the risk of a patient not getting a drug (puts patients first)
• Establishes consistent quality standards and clear expectations for industry
• Anticipates quality problems before they develop to help prevent drug shortages
Office of Biotechnology Products

Divisions not locked into specific products

- Workload Management
- Agility in Response to Market Changes
Definition: Biological Product

- BPCI Act revises the definition of “biological product” in the Public Health Service Act (PHS Act) to include “protein”:
  ... a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product ... applicable to the prevention, treatment, or cure of a disease or condition of human beings ...

- Historically, some proteins have been approved as drugs under section 505 of the FD&C Act (e.g., human growth hormone), and other proteins have been licensed as biologics under section 351 of the PHS Act (e.g., blood factors).
Definition – Protein and Chemically Synthesized Polypeptide

• The term “protein” means any alpha amino acid polymer with a specific defined sequence that is greater than 40 amino acids in size.

• The term “chemically synthesized polypeptide” means any alpha amino acid polymer that (1) is made entirely by chemical synthesis; and (2) is less than 100 amino acids in size.
  – A chemically synthesized polypeptide, as defined, is not a “biological product” and will be regulated as a drug under the FD&C Act unless the polypeptide otherwise meets the statutory definition of a “biological product.”

A Growing OBP Workload Requires Flexibility and Agility

- OBP has review responsibility for proteins that were previously regulated as drugs
- IND and BLA workload for mAbs and related products continues to grow
  - From 2006 through 2010 (5 years), 273 INDs for new products were submitted
  - From 2011 through November 2014 (<4 years), 273 INDs for new products were submitted
    - New products includes INDs for novel and biosimilar mAbs that had not previously been submitted to the FDA
Update on the Biosimilar Program

Quality is the foundation

Additional Clinical Studies

Clin Pharm
Nonclinical

Analytical
Biosimilar Development Programs

• The Center for Drug Evaluation and Research is actively engaging with sponsors regarding biosimilar development. This includes holding development-phase meetings and providing written advice for ongoing development programs.

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

• As of November 30, 2014, 51 programs were in the Biosimilar Product Development (BPD) Program involving the development of biosimilar products to 14 different reference products.
FDA Terminology: Clinical Studies

• 21 CFR 312.21 provides specific definitions for Phase 1, Phase 2 and Phase 3 clinical studies.

• FDA does not think in “Phased Development” terms (Phase 1, 2, and 3 studies) for clinical studies for biosimilar development programs.

• The goal of the clinical studies is not to select a dose or to independently establish safety and effectiveness of the proposed product.
The Question(s) Should Drive the Study Design

- When designing a study, evaluate and understand the question you are trying to answer
  - What is the residual uncertainty?
  - What analytical differences have been observed and how best to evaluate the potential impact?
  - What will the data tell you and will they answer the question?

- Provide a sound rationale for methods, assays, design, analyses, etc.
  - Understand the tool, including any limitations
Plan Your Program

Apply a **step-wise approach** to data generation and the **evaluation of residual uncertainty** *

- Analytical Studies
- Animal Studies
- Clinical PK/PD Studies
- Clinical Immunogenicity Assessment
- Additional Clinical Studies

*The list is not intended to imply that all types of data described here are necessary for any given biosimilar development program. FDA may determine, at its discretion, that certain studies are unnecessary in a 351(k) application.
# Recommended Biosimilar Product Quality Development Process

## Developmental Research
- Purchase reference product lots
- Analyze reference product lots
- Develop biosimilar construct and cell line
- Manufacturing process development

## IND Enabling
- In depth characterization assay development
- Preliminary analytical/functional similarity studies
- Formulation studies
- Analytical and functional similarity studies
- Qualified/validated release and stability assays

## Initial Clinical Studies
- Continuous characterization
- Specification setting
- Final Mf scale
- Stability
- Viral Clearance

## Additional Clinical Studies
- Final analytical and functional similarity studies
- Specification setting
- Stability

## Development Decision
- Biosimilar Initial Advisory Meeting

## BLA
- BPD Type 1/2/3
- BPD Type 4
FDA Terminology: Comparability Versus Analytical Similarity

• **Comparability** generally refers to an assessment of a biological product before and after a manufacturing process change made by a single manufacturer.

• **Analytical similarity** generally refers to an assessment of a proposed biosimilar product in comparison to a US-licensed reference product and to an assessment of a US-licensed reference product to a non-US licensed comparator.
Summary of FDA Advice on Statistics for Analytical Similarity Assessment for a Proposed Biosimilar

• Evaluate quality attributes consistent with the risk assessment principles the ICH Quality Guidelines Q8, Q9, Q10, and Q11.

• Consider criticality risk ranking of quality attributes with regard to their potential impact on activity, PK/PD, safety, and immunogenicity.

• Use a tiered approach for assessment
  – Equivalence testing for some high risk attributes
  – Quality ranges (mean ± X SD) for other high to low risk attributes
  – Raw/graphical comparisons for other attributes

• For advice on individual development programs submit proposal to Agency for feedback

• FDA is considering these issues further and intends to develop guidance for industry as appropriate.
Monoclonal Antibody Development and Engineering Trends
Challenges in Understanding Novel mAb Constructs

• The diversity of mAb related structures continues to increase
  – Antibody-drug conjugates
  – Radiolabeled and other conjugates
  – Fusion proteins
  – mAb fragments
  – Bi- and multi-specific (numerous platforms)
  – Cocktails

• Novel engineering approaches

• Each novel construct will have shared and unique challenges for characterization, formulation, stability and in some cases, manufacturing
Challenges in Understanding Effector Function and Effector Cells

- Most approved mAbs and clinical candidates are intact IgG
  - IgG1, IgG2 and IgG4
- Impact of fucose on IgG1 binding to CD16 (FcγRIIIa) is well understood
  - Focus on ADCC and NK cells
- What is the predominant effector cell type at site of disease?
- How prominent is effector function through CD16 when effector cells express other FcγR? Does fucose matter? (Peipp et al. Blood, 2008; Herter et al. JI 2014)
- Although IgG4 has low effector function, it binds CD64
  - Implications for therapeutic mAbs? (Lux et al. Cell Reports 2014, Swisher mAbs 2014)
- Size of immune complex matters (Lux et al. JI 2013)
- There is growing body of literature showing that under the right conditions, both activating and inhibitory FcγR can have either type of activity (Bartholmaeus et al. JI, 2014 and several others)
Accelerated Developing Programs
### Expedited Programs: a Clinical Decision

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<tr>
<th>Program</th>
<th>Qualifying Criteria: Serious condition and...</th>
<th>Features</th>
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| Fast Track             | - Nonclinical or clinical data demonstrate potential to meet an unmet medical need  
- Or, QIDP             | - Actions to expedite development and review  
- E.g., meetings  
- Rolling review |
| Breakthrough Therapy   | - Preliminary clinical evidence indicates drug may demonstrate substantial improvement on a clinical significant endpoint over available therapies | - All Fast Track features  
- Intensive guidance on efficient drug development  
- Organizational commitment |
| Accelerated Approval   | - Provides meaningful advantage over available therapies  
- Demonstrates effect on surrogate or clinical endpoint that can be measured earlier than IMM | - Approval based on a surrogate or intermediate clinical endpoint reasonably likely to predict clinical benefit |
| Priority Review        | - Would provide a significant improvement in safety or effectiveness  
- Or, other qualifying programs | - Shorter review clock goal for marketing applications  
(6 mo vs 10 mo) |

QIDP = qualifying infectious disease product; IMM = irreversible morbidity or mortality

Table courtesy of A. Pariser and L. Yao
Breakthrough Designation Process

- Need preliminary evidence that the drug may demonstrate substantial improvement over existing therapy on one or more clinically significant endpoints

- Request submitted ideally no later than end-of-Phase 2

- FDA will respond within 60 days of receipt of request
CMC Challenges

• Most critical at early stages, when CMC development is lagging behind clinical development

• Need a plan to acquire process and product understanding at a quicker pace:
  – Manufacturing process development
  – Product understanding, characterization and CQAs
  – Scale-up and comparability exercises
  – Validation plans
  – Commercial plans and process, facilities, stability data and shelf-life
  – Availability at time of launch and continuous supply for the market
  – It is critical to balance the risk to product quality and the availability of therapies for patients in need
BT Opportunities

• FDA may exercise flexibility on certain aspects of the CMC development, however:
  – Products should still meet statutory requirements for approval (safety and effectiveness)

• CMC specific meetings

• Involvement of review and compliance staff

• Plan the BLA submission
  – timeline (rolling review with CMC as first module)
  – potential amendments

• Communication is the key to success:
  – Work collaboratively with the Agency to solve issues early in development
  – Prompt responses to feedback and information request
BT Conclusions and Key Points

• Drugs under expedited programs still need to meet statutory requirement

• Need to meet and sustain market demand

• Early, frequent and transparent communications with the Agency are critical to expedite product development

• Balancing risk to product quality and availability for patients is critical

• FDA is discussing internally ways to exercise some flexibility in terms of quality requirements for products showing high clinical benefits
Lifecycle Approach to Process Validation
Process Validation

• Process Validation is the collection and evaluation of data which establishes scientific evidence that the process is capable of consistently delivering quality product. Process validation involves a series of activities that takes place over the lifecycle of the product and process

• Process validation for drugs (finished pharmaceuticals and components) is a legally enforceable requirement under section 501(a)(2)(B) of the Act (21 U.S.C. 351(a)(2)(B))
Approach to Process Validation

- **Stage 1 – Process Design:** The commercial manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities.

- **Stage 2 – Process Qualification:** During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.

- **Stage 3 – Continued Process Verification:** Ongoing assurance is gained during routine production that the process remains in a state of control.
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Thank you for your attention
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