Regulation of Biotherapeutic Products: U.S. FDA Perspective

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Disclaimer

The views and opinions expressed should not be used in place of regulations, published FDA guidances, or discussions with the Agency.
Outline

- FDA/CDER Office of Pharmaceutical Quality (OPQ)
  - Office of Biotechnology Products (OBP)
- Biologics Regulation and Approval process
  - Investigational new drug (IND) application
  - Biologics Licensing Application (BLA)
    - Standard Approval
    - Expedited Programs
- Regulatory Updates
  - Established conditions
CDER Office of Pharmaceutical Quality

OPQ, which stood-up in January 2015, creates a single unit dedicated to product quality. OPQ promotes “One Quality Voice” through the integration of review, inspection, surveillance, policy, and research for the purpose of strengthening pharmaceutical quality throughout the product lifecycle.
The Office of Pharmaceutical Quality assures that quality medicines are available for the American public.
OBP Products

- Monoclonal Antibodies
- Enzyme Replacement Therapies
- Growth Factors
- Cytokines
- Toxins
- Fc and Fab Fusion Proteins
- Antibody Drug Conjugates

Biological Products not regulated in OBP:
- Vaccines
- Blood Products
- Cellular, Tissue, and gene therapy products
- Allergenic extracts
- Chemically synthesized peptides
- Hormones (e.g., insulin, glucagon, and human growth hormone)
Office of Biotechnology Products

OBP is responsible for the quality review of monoclonal antibodies and most therapeutic proteins at CDER.

*DBRR: Division of Biotechnology Review and Research

# of approved applications (OBP)

* As of August 16, 2016
Team-based Integrated Quality Assessment (IQA)

• Multidisciplinary team
• Integrates review and inspection activities
• Provides aligned patient-focused and risk-based drug product quality recommendations
  – drug substance, drug product, manufacturing, and facilities
• Approximately 13 BLAs have been approved so far employing the IQA approach

Biologics regulation and approval process
Investigational New Drug (IND) Application

- IND application is required to initiate a clinical trial(s) (21 CFR 312)
  - Emphasis is on safety
  - Pre-IND Consultation Program fosters early communications between sponsors and the FDA review divisions.

- Review timeline: 30 calendar days from receipt

- Updates:
  - 157 new product IND reviewed in 2015
  - 165 pre-IND meeting in 2015
  - 2000+ active INDs
  - Pre-IND and IND for proposed biosimilars to 20 different reference products

Guidance for Industry, Content and Format of Phase I Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products, November 1995.
Biologic Licensing Application (BLA)

- **351(a) PHS Act**: “stand alone” biologic
  - Review timeline: 10 months from filing (12 mo from receipt)
  - 16 BLAs filed in 2015
  - 126 approved (351a) BLAs and 25 approved (505b) NDAs

- **351(k) PHS Act**: biosimilar biologic
  - Review timeline: 10 month from receipt
  - 2 approved biosimilar (351k) BLAs

- **Post-approval Supplements**: Changes to an approved application
  - Prior Approval Supplement (PAS): 4 mo from receipt (6 mo for biosimilars)
    - For changes with high risk to impact quality, purity, safety or potency
  - Changes Being Effected (CBE-30/CBE-0): 6 mo from receipt
    - CBE-30: Moderate risk to product quality
    - CBE-0: Minimal risk to product quality
  - ~300 BLA Supplements Reviewed in 2015
Update on Biosimilars

• The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) creates an abbreviated licensure pathway for biological products shown to be biosimilar to or interchangeable with an FDA-licensed reference product.

• Biosimilar or Biosimilarity means:
  – that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components; and
  – there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.
Update on Biosimilars (cont.)

• As of July 31, 2016, there are 62 programs in the Biosimilar Product Development (BPD) Program
  – for 20 different reference products
  – six companies have publicly announced submission of ten 351(k) BLAs to FDA

• Two 351(k) BLAs for biosimilar products have been approved
  – Zarxio (filgrastim-sndz)
  – Inflectra (infliximab-dyyb)

Guidance for Industry: Formal Meetings between the FDA and Biosimilar Sponsors or Applicants
Expedited Programs

- For drugs that address an unmet medical need in the treatment of a serious or life-threatening condition
- Intended to help ensure that therapies for these conditions are approved and available to patients as soon as it can be concluded that the therapies’ benefits justify their risks
- Allow for earlier attention to drugs that have promise in treating such conditions

**Fast Track Designation:** Section 506(b) of FD&C Act added by section 112 of the Food and Drug Administration Modernization Act of 1997 (FDAMA), amended by section 901 of the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA)

**Breakthrough Therapy Designation:** Section 506(a) of the FD&C Act, as added by section 902 of FDASIA, 2012

**Priority Review Designation:** Prescription Drug User Fee Act of 1992

**Accelerated Approval:** Section 506(c) Food, Drug & Cosmetic Act (FD&C Act) of the FD&C Act of 1992, amended by section 901 of FDASIA

Nonclinical or clinical data demonstrate potential to meet unmet medical need

Features:
- Actions to expedite development and review: frequent interactions
- Rolling review (and may be eligible for priority review)
Breakthrough Therapy Designation

• Clinical evidence indicating **substantial improvement** for a clinically significant endpoint over available therapies

• Features:
  – Guidance on efficient drug development
    • Granting 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
  – Organizational commitment
    • 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
    • Involving senior managers and experienced review staff
  – Rolling review
  – Other actions to expedite review (e.g., priority review designation)
Update on Breakthrough products

CDER Actions (through 6/30/2016)
FY 2012: 2 requests, 1 granted, 1 denied
FY 2013: 92 requests, 31 granted, 52 denied
FY 2014: 96 requests, 31 granted, 51 denied
FY 2015: 93 requests, 32 granted, 43 denied
FY 2016: 82 requests, 29 granted, 31 denied

Approvals
CY 2013 – 2015
24 new drug approvals (9 BLAs)
10 supplement approvals (7 BLAs)

CY 2016
6 new drug approvals (1 BLA)
4 supplement approvals (1 BLA)

Accelerated Approval

Approval based on an effect on a surrogate endpoint or an intermediate clinical endpoint that is reasonably likely to predict a drug’s clinical benefit

– Requires post-marketing confirmatory trials to verify the anticipated clinical effect
– Approval of a drug may be withdrawn if trials fail to verify clinical benefit or to demonstrate sufficient clinical benefit to justify the risks associated with the drug

Approvals

CY 2016 (as of 6/30): 4 approvals (1 BLAs)
CY 2015: 8 approvals (2 BLAs)
CY 2014: 8 approvals (3 BLAs)

Biotechnology product approvals include:
Keytruda (pembrolizumab), Blyncito (blinatumomab), Opdivo (nivolumab), Praxbind (idarucizumab), Darzalex (daratumumab), Tecentriq (atezolizumab)

Priority Review Designation

• Would provide a significant improvement in safety or effectiveness

• Features:
  – Shorter clock for review of marketing application compared with standard review
    • 6 (from filing)/8 (from receipt) vs. 10/12 month

Approvals

CY 2015: 7 BLA approvals, 5 of which also had Orphan designation*
CY 2014: 8 BLA approvals, 7 of which also had Orphan designation
CY 2013: 2 BLA approvals, 1 of which also had Orphan designation

* Orphan Designation - Pursuant to Section 526 of the Orphan Drug Act (Public Law 97-414 as amended).

Expedited Development - Challenges

“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.”

e.g., discussions prior to process validation, changes to the manufacturing process and comparability studies, etc.
Experiences and Challenges

• Expedited development requires a strong commitment and careful planning
  – Process development and product characterization need to keep pace with clinical development
  – A commercial manufacturing process needs to be ready to consistently deliver the clinical performance stated on the label and to meet market demand

• Sponsors should request CMC-specific meetings as soon as possible and should plan subsequent meetings carefully

• FDA challenges include resources, expedited review timelines, and some applications for licensure in which product/process knowledge is not as well developed as would be typical for standard development
Regulatory Update: Established Conditions (EC)

Draft Guidance

Established Conditions:
Reportable CMC Changes for Approved Drug and Biologic Products

May 2015

Established Conditions (from the Guidance)

• “The description of the product, manufacturing process, facilities and equipment, and elements of the associated control strategy, as defined in an application, that assure the process performance and quality of an approved product. Changes to the established conditions must be reported to FDA...”

• “Sufficient detail should be provided in the application regarding the proposed established conditions to assure process performance and quality of the approved product.”
Rationale

• BLA, NDA, and ANDA applicants must provide relevant CMC information in the application
  – 21 CFR 601.2
  – 21 CFR 314.50(d)(1) and 21 CFR 314.54(a)(1)

• Information includes
  – Composition of the DP
  – Manufacture of the DS
  – Manufacture of the DP
  – Full description of the manufacturing process (CFR 601.2)
  – Data establishing the stability of the product through the dating period (CFR 601.2)
Rationale

- Changes to an approved application should be reported to FDA
  - 21 CFR 601.12
  - 21 CFR 314.70
- By regulation, only some changes need to be reported
- The EC Guidance is intended to clarify what aspects of an application should be established conditions
Established Conditions: The Control Strategy

Relationship of the Control Strategy to Established Conditions

**Supportive** of product, process, controls, etc.

**Overall** control strategy including facility, environmental controls, etc. (Not typically reported in submission)

Elements **necessary** to assure process performance and product quality
Established Conditions: The Control Strategy (cont.)

- Control strategy elements that could be established conditions (from Draft Guidance)
  - DS/DP (including in-process materials) manufacturing and testing facilities
  - Source of and specifications for starting materials for biological products
  - Process, including in-process tests and sequence of operations, equipment; and process parameters and their ranges
Established Conditions: The Control Strategy (cont.)

– Specifications, including the tests, analytical procedures and acceptance criteria; including specifications for the DS, other components, in-process materials, and the DP.

– Container closure system, components, and specifications.

– Maintenance strategy for chemometric and/or multivariate models (e.g., for models that may have high impact on product quality.)
Established Conditions: The Control Strategy (cont.)

• Elements of the control strategy “not generally considered established conditions”
  – Batch records – however manufacturing changes or changes to the control strategy may require updates to the batch record. Such updated batch records should be submitted to the FDA.
  – Development data
  – Characterization data
  – Validation data
  – Batch analysis data
Changes to Established Conditions

• All changes whether reportable or not should be managed by the sponsor’s quality system

**Foundation:** All changes are managed under the PQS

- Managed *solely* by PQS
- Control Strategy
  - Control Strategy Elements Reported in an Application
  - Established Conditions
  - Changes reportable Post-approval
FDA Perspectives – Potential Benefits of ECs

• Increase transparency
• Reduce submission of unnecessary supplements
  – Effective post approval submission strategies
• Encourage continual process improvements
• Allow FDA to better regulate post approval changes
  – More flexibility/responsibility for manufacturer
  – Risk based principles allow better focus on most important information and changes
  – Clarity for investigators on inspection
Summary

- Biological products are a subset of drugs regulated under provisions of the *Food, Drug and Cosmetic Act* and the *Public Health Service Act* (PHS) Act.

- Biological products are licensed under section 351(a) or 351 (k) of the PHS Act.

- There are four FDA programs intended to facilitate and expedite development and review of new drugs to address unmet medical need in the treatment of a serious or life-threatening condition:
  - fast track designation, breakthrough therapy designation, accelerated approval, and priority review designation.
Summary (cont.)

• Sponsors can request formal meetings with the FDA to seek advice related to the development and review of drugs and biologics, including biosimilars.

• The FDA’s draft guidance on Established Conditions (EC) describes which elements of the control strategy could be considered ECs and would require a post-approval regulatory action (e.g., submission of a supplement) if changed post approval.
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Thank you for your attention

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