US FDA update: Recent Trends in the Regulation of Biopharmaceuticals

CMC Strategy Forum Japan 2017

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Outline

• Office of Pharmaceutical Quality
• CDER’s Emerging Technology Team
• Updates on Biosimilars
• Updates on BsUFA II and PDUFA VI
• Expedited programs
• Established conditions
The Office of Pharmaceutical Quality (OPQ) assures that quality medicines are available for the American public.
**Who reviews the CMC sections of your BLA?**

- OBP has four divisions and operates as a fully integrated unit within OPQ
- OBP is responsible for the quality review of monoclonal antibodies and most therapeutic proteins at CDER

*As of November, 2017, does not include 351(k) BLAs*
Office of Pharmaceutical Quality

- Assure that all human drugs meet the same standards of quality to safeguard clinical performance
- Enhance science- and risk-based regulatory approaches
- Transform product quality oversight from a qualitative to a quantitative and expertise-based assessment
- Provide seamless integration of review, inspection, surveillance, policy, and research across product lifecycle
- Encourage development and adoption of emerging technology
Team-based Integrated Quality Assessment (IQA)

- Multidisciplinary team, maximize team members expertise
- Integrates review and inspection activities
- Provides aligned patient-focused and risk-based drug product quality recommendations
  - drug substance, drug product, manufacturing, and facilities
- Approximately 20 BLAs have been approved so far employing the IQA approach

CDER’s Emerging Technology Team

- A small cross functional team with representation from all relevant CDER review and inspection programs that provides expertise and input for innovative technologies
- Encourage and support the adoption of innovative technology to modernize pharmaceutical development and manufacturing where the Agency has limited review or inspection experience
  - Innovative or novel product technology, manufacturing process, or control strategy
  - Technology has the potential to improve product safety, identity, strength, quality, or purity
  - Existing or planned submission
  - Limited or no regulatory precedent
- Draft guidance provides recommendations to companies that intend to submit CMC information containing emerging technology to FDA
- Contact ETT at CDER-ETT@fda.hhs.gov

Emerging Technology

• Experience with Small Molecule Drugs
  – 3-D Printed Manufacturing (Printed Tablet approved in 2015)
  – Novel Long-Acting Oral Drug Delivery
  – Continuous Manufacturing (PAS approved for oral tablets)

• Biotechnology products
  – Multi-Attribute Methods
  – Next generation sequencing
  – Continuous Manufacturing
  – Advanced Process Controls
Biosimilars: Background

• 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.

• The ability to rely on FDA’s previous finding regarding the reference product to support approval of the biosimilar product allows for a potentially shorter and less costly drug development program.

• Once a biosimilar or interchangeable is approved by FDA, patients and health care providers are able to rely upon the safety and effectiveness of an FDA-approved biosimilar or interchangeable product just as they would for the reference product that the biosimilar was compared to.
Biosimilars Program

• **As of November 1, 2017, 61** programs were enrolled in the Biosimilar Product Development (BPD) Program. CDER has received meeting requests to discuss the development of biosimilars for **27** different reference products

• Since program inception and as of November 1, 2017, **11** companies have publicly announced submission of **20 351(k)** BLAs to FDA

• **Seven 351(k)** BLAs for biosimilar products have been approved.
  – Zarxio (filgrastim-sndz)
  – Inflectra (infliximab-dyyb)
  – Erelzi (etanercept-szsz)
  – Amjetiva (adalimumab-atto)
  – Renflexis (infliximab-abda)
  – Cyltezo (adalimumab-adbm)
  – Mvasi (bevacizumab-awwb)
FDA Biosimilars Guidance

1. Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (final, 2015)
2. Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product (final, 2015)
4. Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants (final, 2015)
5. Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product (final, 2016)
8. Labeling for Biosimilar Products (draft, 2016)
9. Considerations in Demonstrating Interchangeability With a Reference Product (draft, 2017)
10. Statistical Approaches to Evaluate Analytical Similarity (draft, 2017)

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm290967.htm
Guidance Documents updates

• 2017 Final Guidance
  – Nonproprietary Naming of Biological Products

• 2017 Draft Guidance
  – Considerations in Demonstrating Interchangeability With a Reference Product Guidance for Industry
  – Statistical Approaches to Evaluate Analytical Similarity

• BsUFA II commitments
  – Finalize draft guidance for interchangeability, statistical approaches and labeling for biosimilar biological products
  – Publish draft guidance “Processes and further considerations related to post-approval manufacturing changes for biosimilar biological products”
  – Revise guidance on “Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants” and update guidance on “Best Practices for Communication Between IND Sponsors and FDA During Drug Development”
BsUFA II Highlights

• BsUFA II adopted “The Program” review model for **all** original 351(k) BLAs – similar to “The Program” under PDUFA for NME NDAs and original 351(a) BLAs
  – The purpose in adopting “The Program” as part of BsUFA II is to promote the efficiency and effectiveness of the first cycle review process and minimize the number of review cycles

• BsUFA II includes modifications for FDA and sponsor meeting management
  – Reduced Scheduling Timeframe for Biosimilar Initial Advisory Meetings (BIA) (From 90 to 75 days from receipt of meeting request and package)
  – Increased Scheduling Timeframe for Biosimilar Product Development (BPD) Type 2 Meetings (From 75 to 90 days from receipt of meeting request and package)
  – Preliminary responses to meeting questions provided no later than 5 days before BPD Type 2 and Type 3 meetings
  – Sponsors may request Written Responses only for BIA and BPD Type 2 meetings
  – FDA cannot convert the meeting type. If FDA determines that a face-to-face/teleconference is not necessary, FDA will deny the meeting and the sponsor will need to submit a new request as a WRO. Same thing for when a WRO is submitted but FDA determines a face-to-face/teleconference is needed.

• BsUFA II Enhancement for Prior Approval Manufacturing Supplements
  – Prior-approval manufacturing supplements will be reviewed in 4 months instead of 6 months to align with PDUFA VI
  – CBE-0 and CBE-30 manufacturing supplements will continue to be reviewed in 6 months
BsUFA II Highlights

• BsUFA II permits goal extensions for missing manufacturing information
  – All original applications and supplements are expected to include a comprehensive and readily located list of manufacturing facilities
  – If FDA identifies the need to inspect a facility that was not included on the list, the Agency may extend the goal date as follows:
    • 3 months for an original application or efficacy supplement, or
    • 2 months for a manufacturing supplement
  – Only one extension is permitted per review cycle (e.g., either major amendment clock extension or facilities clock extension)
  – Approach consistent with PDUFA VI
PDUFA VI Highlights

• Pre submission meeting
  – FDA and applicant have the option to agree on a Formal Communication Plan that may or may not include Program elements and interactions that are not part of the Program

• Expedited reviews: Current practices regarding Program flexibility for expedited reviews are now part of PDUFA VI
  – For applications that received priority review, the review team plans to act at least one month before the PDUFA goal date, provided no significant application deficiencies prevent an early action.
  – The decision to perform an expedited review of an application is independent of decisions regarding FDA’s expedited programs (e.g., fast track designation, breakthrough therapy designation, accelerated approval, and priority review) programs
  – Intention to perform an expedited review is notified in the 74 day letter
  – If significant deficiencies are identified by the review team at any time during an expedited review, FDA can revert, for the remainder of the review, to the usual timelines for priority review
PDUFA VI Highlights

• PDUFA VI includes modifications for FDA and sponsor meeting management
  – New Type B (EOP) meeting
    • Scheduled 70 calendar days from receipt
    • Background package received 50 calendar days before the date of the meeting or expected written response
    • Preliminary comments provided no later than 5 days before Type B (EOP) meeting
    • Industry responses provided no later than 3 days after receipt of preliminary comments
  – Earlier receipt of meeting package for Type C meetings (from 30 to 47 days before the date of the meeting or expected written response)
  – Sponsors may request Written Responses for any meeting type (Type A, Type B, Type B(EOP), Type C)
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


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

Fast Track Designation

• Nonclinical or clinical data demonstrate potential to meet unmet medical need

• Features:
  – Actions to expedite development and review: frequent interactions with review team
  – Rolling review
  – Eligibility for Accelerated approval and priority review

Data from fiscal year 1998-2016

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

Priority Approvals

CY 2016: 3 BLA approvals, 1 of which also had Orphan designation*
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).
Accelerated Approval

Approval based 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

Accelerated Approvals

CY 2017: 3 approvals (1 BLAs)
CY 2016: 7 approvals (2 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), Lartruvo (olaratumab), Bavencio (avelumab)

Breakthrough Therapy Designation

- Clinical evidence indicating **substantial improvement** for one or more clinically significant endpoint over available therapies

- Features:
  - Guidance on efficient drug development
    - Increasing frequency of meetings throughout the development of the drug
    - Providing timely advice to facilitate an efficient development program
    - 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 team lead to facilitate an efficient review, coordinate internal and external communications
    - Involving senior managers and experienced review staff
  - Rolling review
  - Other actions to expedite review (e.g., priority review designation)
Update on Breakthrough products

CDER BT requests received:

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Marketing Approvals

CY 2012: No approvals
CY 2013 – 2015: 24 new drug approvals (9 BLAs); 10 supplement approvals (7 BLAs)
CY 2016: 6 new drug approvals (3 BLAs); 12 supplement approvals (7 BLAs)
CY 2017*: 16 new drug approvals (6 BLAs); 10 supplement approvals (5 BLAs)

* 2017 data through September 30, 2017

“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.
Expedited Development - Challenges

• Alignment of CMC development timelines with clinical development
  – Commercial manufacturing process ready to enable product availability at time of launch and continuous supply for market demand
  – Early availability of manufacturing and testing sites for inspection
• Accelerated manufacturing development
  – less product/process experience
  – Limited data (batch, stability) available at time of submission
  – risk-benefit assessment regarding risk of less CMC information vs. patient benefit
• Review timing constraints
• Supply/availability considerations

• General CMC requirements and expectations do not change
• Products should still meet statutory requirements for approval (safety and effectiveness)
Expedited Development- Lessons learned

• Robust product characterization and understanding of CQAs are critical

• Keep development as simple as possible. Minimize changes
  – Reduce the numbers of comparability studies:
    • manufacturing changes, scale-up and comparison to clinical process
    • can you launch from the clinical site? (considerations of market need and mitigation of shortages)
  – Limit number of DP formats and formulation changes
  – Limit number of initial manufacturing sites in the BLA
  – Include as many lots as possible in the clinical studies

• Additional sites, DP formats etc. can be added to the license after BLA approval
Naming of Biological products

• Nonproprietary name (proper name): core name + four lowercase letters suffix devoid of meaning

• Same core name (USAN Council, when available) for originator, related, biosimilar or interchangeable biological products to indicate relationship between products

• Apply to biological products licensed under the PHS Act

• Considerations:
  – Enhance pharmacovigilance
  – Facilitate accurate identification of biological products by health care practitioners and patients
  – help minimize substitution of products that have not been determined to be interchangeable
  – avoid inaccurate perceptions of the safety and effectiveness of biological products based on their licensure pathway.

• Applicant should propose up to 10 suffixes composed of four lowercase letters and supporting analysis of the proposed suffixes

• First novel biologic with a suffix: MEPSEVII (vestronidase alfa-vjbk) approved November 15, 20017

• Second: HEMLIBRA® (emicizumab-kxwh) approved November 16, 2017

Established Conditions


• The Guidance is intended to clarify what aspects of an application should be established conditions or “regulatory commitments’

• “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: 21 CFR 600’s and 300’s
Established Conditions

• ECs are:
  Composition of DP, DS/DP manufacturing and testing facilities; source and specifications for starting materials for biological products; process, including in-process tests and sequence of operations, equipment, and process parameters and their ranges; specifications, stability data for dating period, etc.

• ECs are not:
  Batch records (but if a change to the control strategy impacts the BR, a current BR should be provided in the appropriate regulatory submission), Development data; Characterization data; Validation data; Batch analysis data; etc.

• Where they are commonly located in the CTD

• “The relevant information would still be considered an established condition even if it is located in a CTD section not specified below [in the list that follows].”

• ECs are a major component of ICH Q12. Delineation of ECs in a submission allows efficient change management during product lifecycle
Established Conditions, control Strategy and change management

- **Overall** control strategy including facility, environmental controls, etc. (Not typically reported in submission)
- **Supportive** of product, process, controls, etc.
- **Elements necessary** to assure process performance and product quality
- **Changes managed solely** by PQS
- **Changes reportable** Post-approval

All Changes whether reportable or not should be managed under the Sponsor’s PQS
ICH Q12 Lifecycle Management

• “This guideline is intended to work with ICH Q8 to Q11 Guidelines and will provide a framework to facilitate the management of post-approval Chemistry, Manufacturing and Controls (CMC) changes in a more predictable and efficient manner across the product lifecycle.

• Adoption of this guideline will promote innovation and continual improvement, and strengthen quality assurance and reliable supply of product, including proactive planning of supply chain adjustments.

• “Introduce the concept of a post-approval management plan that can be used to proactively identify post-approval changes and the mechanism to submit and assess these changes by regulatory authorities (Assessors and Inspectors)”

• “Establish criteria for post-approval change management protocols that can be adopted by the ICH regions (enabling a harmonised proactive approach for lifecycle management)”

• “Encourage enhanced product development and control strategy approaches (Quality by Design (QbD)) providing opportunities for scientific and risk based foundations for post-approval change management plans”
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