US FDA Update: Recent Trends in the Regulation of Biopharmaceuticals

CMC Strategy Forum Japan 2018

Will Hallett
Division of Biotechnology Review and Research II
Office of Biotechnology Products
OPQ, CDER, FDA

December 2018
Disclaimer

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

• Office of Pharmaceutical Quality
• Updates on Biosimilars
• Expedited programs
The Office of Pharmaceutical Quality (OPQ) assures that quality medicines are available for the American public.
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
OPQ Strategic Priorities 2018

- Strengthen OPQ’s Collaborative Organization
  - Leverage a collaborative culture, an engaged and empowered workforce, streamlined processes, and effective teaming to ensure an efficient, high-performing, innovative, and results-oriented organization

- Promote Availability of Better Medicines
  - Minimize barriers to encourage innovation within FDA and in the pharmaceutical sector through sensible oversight, research, risk-based decision-making, and continuous improvement

- Elevate awareness and commitment to the importance of pharmaceutical quality
  - Effectively communicate the importance of quality and that the American public can trust their drugs

- Strengthen partnerships and engage stakeholders
  - Build productive relationships with business partners within and outside FDA and jointly foster effective stakeholder engagement to meet the needs of 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

*DBRR: Division of Biotechnology Review and Research

*As of October 2018, does not include 351(k) BLAs
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
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 October 1, 2018, 63 programs were enrolled in the Biosimilar Product Development (BPD) Program. CDER has received meeting requests to discuss the development of biosimilars for 31 different reference products.

- Since program inception and as of October 1, 2018, 12 companies have publicly announced submission of 25 351(k) BLAs to FDA.

- As of November 2, 2018, thirteen 351(k) BLAs for biosimilar products have been approved.
  - Zarxio (filgrastim-sndz)
  - Erelzi (etanercept-szss)
  - Renflexis (infliximab-abda)
  - Mvasi (bevacizumab-awwb)
  - Ixifi (infliximab-qbtx)
  - Fulphila (pegfilgrastim-jmdb)
  - Udenyca (pegfilgrastim–cbqv)
  - Inflectra (infliximab-dyyb)
  - Amjevita (adalimumab-atto)
  - Cyltezo (adalimumab-adbm)
  - Ogivri (trastuzumab-dkst)
  - Retacrit (epoetin alfa-epbx)
  - Nivestym (filgrastim-aafi)
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) (withdrawn)
5. Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product (final, 2016)
8. Labeling for Biosimilar Products (final, 2018)

10. Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act (draft, 2014)

11. Implementation of the “Deemed to be a License” Provision of the BPCI Act of 2009 (draft, 2016)

12. Considerations in Demonstrating Interchangeability With a Reference Product (draft, 2017)


14. Formal Meetings Between the FDA and Sponsors or Applicants of BsUFA Products (draft, 2018)

Development of Future Guidance

- FDA has committed to publish draft, revised draft, or final guidance describing the following:
  - *Statistical Approaches to Evaluate Analytical Similarity* (draft guidance published September 2017; revised draft or final guidance by 5/21/19)
  - *Considerations in Demonstrating Interchangeability With a Reference Product* (draft guidance published January 2017; revised draft or final guidance by 5/19/19)
  - Processes and further considerations related to post-approval manufacturing changes for biosimilar biological products (draft guidance by 3/31/19)
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

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:

<table>
<thead>
<tr>
<th>Fiscal Year</th>
<th>Requests</th>
<th>Granted</th>
<th>Denied</th>
<th>Withdrawn</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2013</td>
<td>92</td>
<td>31</td>
<td>52</td>
<td>9</td>
</tr>
<tr>
<td>2014</td>
<td>96</td>
<td>31</td>
<td>51</td>
<td>14</td>
</tr>
<tr>
<td>2015</td>
<td>93</td>
<td>32</td>
<td>43</td>
<td>18</td>
</tr>
<tr>
<td>2016</td>
<td>106</td>
<td>46</td>
<td>48</td>
<td>12</td>
</tr>
<tr>
<td>2017</td>
<td>111</td>
<td>50</td>
<td>49</td>
<td>12</td>
</tr>
<tr>
<td>2018</td>
<td>139</td>
<td>51</td>
<td>50</td>
<td>16</td>
</tr>
</tbody>
</table>

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)
CY 2018*: 11 new drug approvals (6 BLAs); 14 supplement approvals (7 BLAs)

* 2018 data through September 30, 2018

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 2017: 9 BLA approvals, 5 of which also had Orphan designation*
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 2018: 6 approvals (3 BLAs)
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), Blincyto (blinatumomab), Opdivo (nivolumab), Praxbind (idarucizumab), Darzalex (daratumumab), Tecentriq (atezolizumab), Lartruvo (olaratumab), Bavencio (avelumab)

**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.
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
Acknowledgements

Howard Anderson
Chana Fuchs
Susan Kirshner
Marjie Shapiro
Kurt Brorson
Leah Christl
Leslie Rivera-Rosado
Emanuela Lacana
Cristina Ausin-Moreno
Sarah Kennett
Ingrid Markovic

Thank you
William.Hallett@fda.hhs.gov