FDA Regulatory Updates

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CASSS Japan
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Overview

• Biosimilars
• Established Conditions
• Breakthrough Therapies
Biosimilars

• To date
  – FDA approved one 351(k) BLA for a biosimilar product, Zarxio (filgrastim-sndz).
  – There are four companies that publicly announced they submitted a total of five applications (351(k) BLAs)

• As of July 31, 2015, 57 programs were in the Biosimilar Product Development (BPD) program for 16 different reference products.

• An additional 27 programs have had an initial advisory meeting with FDA
Biosimilars

• On April 28, FDA published the following final guidances:
  – Scientific Considerations in Demonstrating Biosimilarity to a Reference Product
  – Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product
Biosimilars

• FDA previously published the following draft guidances:
  – Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants
  – Biosimilars: Additional Questions and Answers Regarding Implementation of the BPCI Act of 2009
  – Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product
  – Reference Product Exclusivity for Biological Products Filed Under Section 351 (a) of the PHS Act
  – Nonproprietary Naming for Biological Products
Biosimilars

• FDA expects to issue the following draft guidances in 2015 as reflected on the CDER Guidance Agenda:
  – Considerations in Demonstrating Interchangeability to a Reference Product
  – Statistical Approaches to Evaluation of Analytical Similarity Data to Support a Demonstration of Biosimilarity
  – Labeling for Biosimilar Biological Products
Definition of Biosimilarity

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.

Reference Product means the single biological product licensed under 351(a) of the PHS Act

Section 7002(b)(2) of the Affordable Care Act, amending section 351(i) of the PHS Act.
Summary of FDA Advice on Statistics for Analytical Similarity Assessment for a Proposed Biosimilar

- Perform a risk assessment of quality attributes
- 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 the 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
Clarification of Criticality Risk Ranking and Statistical Tiers

- The criticality risk ranking approach is the same for NBES and biosimilars
- Many attributes will be ranked as critical or highly critical
- FDA does not intend all high risk attributes to be tested using the most rigorous statistical method.
- In general, assays that assess mechanisms of action should be evaluated using Tier 1 statistical methods
- Protein content as a Tier 1 method
  - When the product has a narrow therapeutic index;
  - When dosing is on the linear portion of the response curve;
  - Would not be included in Tier 1 for products such as mAbs or enzymes, which are dosed to saturation.
FDA intends to consider the **totality of the evidence** provided by a sponsor and recommends a **stepwise approach to demonstrating biosimilarity**, which can include a comparison of the proposed biosimilar product and the reference product with respect to structure, function, animal toxicity, human pharmacokinetics (PK) and pharmacodynamics (PD), clinical immunogenicity, and clinical safety and effectiveness.
Product Development

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, in its discretion, that certain studies are unnecessary in a 351(k) application.

From: “Biosimilars in the US: Learning from the first application and future outlook” by Leah Christl, PhD. EBG meeting. April, 2015
First Marketing Application (351(k) BLA) for a Biosimilar in the U.S.
Proposed Biosimilar to Neupogen (filgrastim)


- Sandoz requested licensure of EP2006 as a biosimilar to US-licensed Neupogen for all of the 5 indications for which US-licensed Neupogen was previously licensed.

- The “Interchangeability” designation was not requested by Sandoz.


### Studies to Support Biosimilarity

<table>
<thead>
<tr>
<th>Analytical</th>
<th>PK/PD Similarity</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>• EP2006</td>
<td>• EP06-101</td>
<td>• EP06-301</td>
</tr>
<tr>
<td>• US-licensed Neupogen</td>
<td>• EP06-102</td>
<td>• EP06-302</td>
</tr>
<tr>
<td>• EU-approved Neupogen</td>
<td>• EP06-103</td>
<td></td>
</tr>
<tr>
<td>• EP06-105</td>
<td>• EP06-105</td>
<td></td>
</tr>
<tr>
<td>• EP06-109</td>
<td>• EP06-109</td>
<td></td>
</tr>
</tbody>
</table>

- All studies, except EP06-109 and EP06-302 used a Neupogen product that had been approved by the European Union (EU-Neupogen) as active comparator
- A scientific bridge needs to be established to support use of EU-Neupogen as active comparator

Immunogenicity was assessed in PK/PD and clinical studies

Analytical Studies
Analytical Similarity Summary


<table>
<thead>
<tr>
<th>Quality Attribute</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary structure</td>
<td>Same amino acid sequence</td>
</tr>
<tr>
<td>Bioactivity</td>
<td>Highly Similar</td>
</tr>
<tr>
<td>Protein content</td>
<td>Highly Similar</td>
</tr>
<tr>
<td>Receptor binding</td>
<td>Highly Similar</td>
</tr>
<tr>
<td>Clarity</td>
<td>Highly Similar</td>
</tr>
<tr>
<td>Sub-visible particles</td>
<td>Highly Similar</td>
</tr>
<tr>
<td>Secondary and tertiary structure</td>
<td>Highly Similar</td>
</tr>
<tr>
<td>High molecular weight variants/aggregates</td>
<td>Highly Similar</td>
</tr>
<tr>
<td>Oxidized species</td>
<td>Highly Similar</td>
</tr>
<tr>
<td>Covalent dimers</td>
<td>Highly Similar</td>
</tr>
<tr>
<td>Partially reduced species</td>
<td>Highly Similar</td>
</tr>
<tr>
<td>fMet1 species</td>
<td>Highly Similar</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Quality Attribute</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sequence variants:</td>
<td>Highly Similar</td>
</tr>
<tr>
<td>His→Gln</td>
<td></td>
</tr>
<tr>
<td>Asp→Glu</td>
<td></td>
</tr>
<tr>
<td>Thr→Asp</td>
<td></td>
</tr>
<tr>
<td>Succinimide species</td>
<td>Highly Similar</td>
</tr>
<tr>
<td>Phosphogluconoylation</td>
<td>Highly Similar</td>
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<tr>
<td>Acetylated species</td>
<td>Highly Similar</td>
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<tr>
<td>N-terminal truncated variants</td>
<td>Highly Similar</td>
</tr>
<tr>
<td>Norleucine species</td>
<td>Highly Similar</td>
</tr>
<tr>
<td>Deamidated species</td>
<td>Highly Similar</td>
</tr>
</tbody>
</table>

* For product-related species, “highly similar” means same type and levels of the species under evaluation

In addition, the three products have highly similar stability profiles

Statistical Equivalence Test for Bioactivity

The biological activity of the three products is statistically equivalent (mean value)

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>(-8.67, -2.27)</td>
<td>(-5.47, 0.54)</td>
<td>(-6.34, 0.10)</td>
</tr>
</tbody>
</table>

(-9.32, 9.32)

(-10.07, 10.07)

(-9.32, 9.32)

Results support analytical similarity and the analytical bridge

Analytical Similarity

Conclusions

Analytical Similarity Conclusions

• Extent of analytical characterization of EP2006 and comparator products (US-licensed Neupogen and EU-approved Neupogen) is robust

• EP2006 clinical and commercial product is analytically “highly similar” to US-licensed Neupogen

• Analytical similarity data do not raise residual uncertainties about the similarity of EP2006 and US-licensed Neupogen. The impact of the EP2006 formulation on PK/PD will be addressed in the non-clinical and clinical studies
FDA Conclusions

• The data submitted by Sandoz demonstrated that
  – EP2006 is highly similar to US-licensed Neupogen, and
  – that there are no clinically meaningful differences between the two products.

• In addition, the totality of evidence supported that EP2006 should be granted licensure as a biosimilar product for all 5 of the indications for which US-licensed Neupogen was previously licensed.
Learnings from First Marketing Application
Applicant Submissions

• Analytical data is the foundation
  – Address observed differences between products with data
  – Provide a sound rationale for methods, assays, analyses, etc.
  – Consider source and potential impact of residual uncertainty

• When designing a study, evaluate and understand the question you are trying to answer
  – How best to evaluate the potential impact of observed differences
  – What will the data tell you
Applicant Submissions

- Evaluate plan to support extrapolation early in development
  - Differences between conditions of use do not necessarily preclude extrapolation, but differences need to be addressed

- Ensure totality of the evidence, including scientific justification for extrapolation
  - Present data in step-wise framework – tell “biosimilarity story”

From: “Biosimilars in the US: Learning from the first application and future outlook” by Leah Christl, PhD. EBG meeting. April, 2015
New Concepts for Advisory Committees and Healthcare Community

• Need to change the focus and the conversation:
  – The goal of a biosimilar development program is to demonstrate biosimilarity between the proposed product and a reference product, not to independently establish safety and effectiveness of the proposed product.
  – Move away from concept of “pivotal Phase 3” safety and effectiveness study paradigm
New Concepts for Advisory Committees and Healthcare Community

• Need to better explain and educate about:
  – analytical similarity data (structural and functional analysis)
  – PK and PD (if relevant) endpoints are generally more sensitive to product differences than traditional clinical efficacy endpoints
  – extrapolation

From: “Biosimilars in the US: Learning from the first application and future outlook” by Leah Christl, PhD. EBG meeting. April, 2015
New Draft Guidance
Established Conditions: Reportable Changes for Approved Drug and Biologic Products
Established Conditions

• *“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…”

Established Conditions

• “…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 CFR314.50(d)(1) and 21 CFR314.54(a)(1)

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

• Changes to an approved application should be reported to FDA
  – 21 CFR 601.12
  – 21 CFR 314.70(a)

• By regulation only some changes need to be reported

• The 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
Established Conditions: The Control Strategy

- Control strategy elements that could be established conditions (from 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
Summary

• FDA published the Draft Guidance for Industry Established Conditions: Reportable CMC Changes for Approved Drug and Biologic Products (May 2015)

• The guidance provides clarification on what changes should be reported to FDA

• Changes to a biologics license should be evaluated per 21 CFR 601.12 and reported accordingly
Breakthrough Therapies
Considerations for Expedited Programs*

Addressing unmet medical needs in the treatment of a serious condition:

– Serious condition
  • The statutory and regulatory eligibility criteria for expedited programs require that a drug be intended to treat a serious condition.

– Unmet medical need
  • Condition whose treatment/diagnosis is not adequately addressed by available therapy.

– Available Therapy
  • Approved/licensed in the United States for the same indication and relevant to U.S. standard of care for the indication.

* FDA Guidance for Industry:
Expedited Programs for Serious Conditions – Drugs and Biologics
Expedited Development Programs

• Fast Track Designation*
  – Frequent interaction with review team
• Potential for Priority review if supported by clinical or non-clinical data
  – Rolling BLA/NDA review

*FDASIA Title IX, Section 901 (2012); FDAMA 1997; 506(b) Food Drug and Cosmetics Act
Expedited Development Programs

• Accelerated Approval Pathway*
  – Surrogate endpoint reasonably likely to predict clinical benefit
  – Clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality, reasonably likely to predict an effect
  – Sponsor must agree to conduct post-marketing confirmatory trials

*FDASIA Title IX, Section 901 (2012); 506(c) Food Drug and Cosmetics Act; 21 CFR part 314 subpart H; 21 CFR 601 subpart E
Expedited Development Programs

• Breakthrough Therapy Designation
  – Breakthrough drug “…preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints,…”
  – Serious and life threatening condition

*FDASIA Title IX, Section 902 (2012); 506(a) Food Drug and Cosmetics Act
Expeditied Development Programs

• Breakthrough Designation Process
  – Need preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapy on one or more clinically significant endpoints
  – Request submitted any time during IND, or with the BLA or NDA application, ideally prior to end-of-Phase 2
  – FDA will respond within 60 days of receipt of request
Expedited Review Program

• *Priority Review
  – Drug that treats a serious condition and if approved would provide significant improvement in safety and effectiveness
  – Shortens the review timeline from 10 to 6 months
  – Sponsor can request priority review with original NDA/BLA
    • FDA grants priority review within 60 days of submission, assigned at time of filing.

*PDUFA 1992
Expedited Review

- Expedited Reviews are:
  - A subset of priority reviews, and
  - Action is planned for at least one month prior to PDUFA goal date, if:
    - No unexpected review issues arise
    - Review team does not experience unexpected shift in work priorities or staff
  - CDER staff will consider an expedited review for each marketing application for BTD drugs

*MAPP 6025.7 Good Review Practice: Review of Marketing Applications for Breakthrough Therapy-Designated Drugs and Biologics That Are Receiving an Expedited Review*
Breakthrough Therapies: FDA Actions for Expedited Development*

- Increased frequency of meetings/communications
- Timely advice to facilitate an efficient development program
- Senior management involvement
  - Division Directors, Office Directors, Center leadership where appropriate
- Cross Disciplinary Team Leader
  - Coordinates internal and external communication in collaboration with the Regulatory Project Manager
- Experienced review staff

*These are requirements per FDASIA provisions.
Breakthrough Therapies: FDA Actions for Expedited Review

- Rolling review agreement
- Priority review designation
  - Consideration to further expedite the review
Breakthrough Therapy Requests Submitted to CDER

Breakthrough Therapy Requests – CDER (through 4/3/15)
A Conversation About Risk…
Expectations for Quality

Patients and caregivers assume that their drugs:

• Are safe
• Are efficacious
• Have the correct identity
• Deliver the same performance as described in the label
• Perform consistently over their shelf life
• Are made in a manner that ensures quality
• Will be available when needed
What is Pharmaceutical Quality?

• The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as identity, potency, and purity (ICH Q6B)

• The degree to which a set of inherent properties of a product, system or process fulfills requirements (ICH Q9)
Challenges for Expedited Development

• Alignment of CMC development timelines with clinical development
  – Consideration of manufacturing scale
  – Coordination with contract manufacturers, as needed
  – Early availability of manufacturing sites for inspection

• Accelerated manufacturing development likely with less information than typically available
  – May warrant a risk-benefit assessment regarding risk of less CMC information vs. patient benefit
Considerations for Expedited Reviews

• Limited data available and/or submitted
  – Manufacturing batch data
  – Stability data
  – Data available at time of submission
• Review timing constraints
• Frequent communication often needed
• Supply/availability considerations

All rest on the overall risk to quality as well as potential mitigation strategies.
Breakthrough Therapies – Product Quality

– Products should still meet statutory requirements for approval
  • safety and effectiveness

– Sponsors should be prepared to develop all aspects of the program at a more rapid pace
  • CMC should not be lagging behind
Expedited CMC development: How do we get there?

- Initiate communications as early as possible following BT designation
- The goal is to facilitate and expedited development through the IND phase
- Work collaboratively with the Agency to solve issues early in development and in the process
- Receive prompt responses to feedback and information request
- Submit the relevant data necessary for the Agency to make a scientific, risk based assessment to ensure availability of quality product at the time of BLA approval
Considerations for Plans Submitted Under IND

- Proposed development timelines, activities, and validation plans
- Formulation changes, manufacturing changes, scale-up and comparison to clinical process
- Physico-chemical comparability of lots used in clinical studies and commercial lots or a plan to establish analytical comparability
- Bridging information needed
Considerations for Plans Submitted Under IND

- Product Characterization
- Critical quality attributes
- Control strategies
- Stability strategies and stability studies needed to support the proposed shelf-life
- Drug product dosage form
- Administration instructions, final packaging and delivery systems (e.g. vials, pre-filled syringes, etc.)
- Manufacturing and testing site readiness for clinical and marketed products
OBP Experience with BT products

• Products licensed with breakthrough indications:
  – Obinutuzumab, Pembrolizumab, Blinatumomab, Nivolumab, Asphatase alfa; Aflibercept; Ranibizumab

• INDs
  – OBP is developing experience with products in early development
OBP Experience with BT INDs

- For one IND:
  - review team had monthly communication with sponsor through amendments requiring FDA feedback, and with meetings
  - Multiple comparability studies, including new manufacturing sites and a new DP presentation.
  - Plans for post-approval manufacturing changes were identified.
- Most BT INDs have not required monthly communications, but have had more frequent communications than for other INDs.
- Agreements reached for development and validation plans.
*Data reflect the 20 BT drugs that received BT designation during their IND phase and that submitted a marketing application by the end of FY2014. Note that CDER-sponsor interactions typically increase even for non-BT applications prior to the submission of a marketing application.

**General Advice Letters and Information Requests issued by the FDA to the sponsor

***Sponsor responses to FDA Information Requests

****Type B meetings between the FDA and sponsor
OBP Experience with BT Products

• For the shorter BT BLA review timeline, OBP assigns multiple reviewers to one BLA. Experienced reviewers are targeted.

• For one highly expedited BT review, the OBP review team included*:
  – 5 reviewers (DS, DP, assays, labeling, facility inspector)
  – 2 Team Leaders
  – 1 Review Chief

*for regular BLAs, one to two reviewers, a single TL and a Review Chief make up an OBP review team.
Lessons Learned

• Robust product characterization and understanding of CQAs are critical in BLAs, including BT products.

• Keep it 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

• Additional sites, DP formats etc. can be added to the license after BLA approval.
Lessons Learned

For BLA still require:

- Validation of the manufacturing process
- Validation of analytical assays
- Microbial control and sterility assurance, for sterile drugs
- Viral clearance
- Relevant stability data to enable assignment of expiration dating

• Manufacturing and testing sites have to be ready for inspection

• Enable product availability at time of launch and continuous supply for the market
Lessons Learned

• Limit variabilities and changes not necessary for launch. E.g.
  • What is the container closure system? Single container closure system vs. Multiple DP formats, container closure systems

• Early planning can result in need for fewer:
  – Development data (e.g., comparability studies, formulation studies)
  – Validation data (single vs. duplicate sites)
  – Container closure information/data
  – Stability data
  – Required inspections during BLA
Conclusions

• Patients and caregivers expect quality
  – Safe, effective, high quality, correct identity, perform as labelled, available

• Pharmaceutical quality
  – Expectations the same regardless of submission strategy

• Challenges with expedited/breakthrough therapies
  – Alignment of CMC and clinical development
  – Often warrant a risk/benefit assessment regarding risk of less CMC information vs. patient benefit

• Proactive communications regarding risk management encouraged during development and review

• Best practices focus on the identification of opportunities for early submission and/or dialog, as well as effective communication of risk to quality
BTD Approvals

- KALYDECO
- ESBRIEET
- SOVALDI
- GAZYVA
- RAPAMUNE
- IMBRUVICA
- OPDIVO
- IBRANCE
- EYLEA
- VIERIRA PAK
- ZYKADIA
- OFEV
- ZYDELIG
- HARVONI
- BLINCYTO
- ARZERRA
- PROMACTA
- LUCENTIS
Many, many, thanks…

- Leah Christl
- Chana Fuchs
- Maria Teresa Gutierrez-Lugo
- Sarah Kennet
- Emanuela Lacana
- Sarah Pope Miksinski
- Miranda J Raggio
BTD Program Resources

**MAPP 6025.6: Good Review Practice: Management of Breakthrough Therapy-Designated Drugs and Biologics**
http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm

**MAPP 6025.7: Good Review Practice: Review of Marketing Applications for Breakthrough Therapy-Designated Drugs and Biologics That Are Receiving an Expedited Review**

**Guidance for Industry: Expedited Programs for Serious Conditions—Drugs and Biologics:**
BTD Program Resources-2

MAPP 6030.9: Good Review Practice: Good Review Management Principles and Practices for Effective IND Development and Review

BT Information on fda.gov:

Section 902 of FDASIA: