Table 36: Biosimilars: Ways to Manage Challenges Post-approval

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SCOPE:

By the end of 2016, four biosimilars — including several mAb products — had been approved in the U.S., which is expected to be their major market. Major regulatory agencies, including the FDA, European Medicines Agency (EMA), Health Canada, Australia’s Therapeutic Goods Administration (TGA), and Japan’s Pharmaceuticals and Medical Devices Agency (PMDA), have released guidelines on biosimilar development. In most cases, these guidelines are quite similar. But there are some differences that can challenge companies post-approval. Once approved, biosimilars are considered stand-alone products and life cycle management is not different than those considerations for innovator drugs. What are the best practices for post approval change management?

QUESTIONS FOR DISCUSSION:

1. What processes are in place in your organization to assess the risk and determine paths to justify post-approval changes, for example?
   a. Changes to control system (e.g. specifications, analytical methods)
   b. Changes to manufacturing processes due to improvements or limitations by process transfer
      i. Cell-lines
      ii. Purification
      iii. Implementation of disposable technologies

2. Use of ICH Q5E as guidance for comparability
   a. What are the challenges of implementing post-approval changes in ICH regions versus non-ICH regions? Provide examples.
      i. Requirements for safety and efficacy assessments
      ii. Timelines
      iii. Comparability packages


NOTES:

1) Processes in place at different organizations for post-approval changes
   – Would follow comparability principles based on ICH guidelines. Perform risk assessments, similar to what is done for any other process changes.
   – Submit comparability protocol, obtain approval and execute.
   – How to address some structural differences? How do you demonstrate comparability?
• If major process change to biosimilar, submission is expected to show no impact to clinical profile. Input from regulator? Would there be additional requirements? Would the science behind comp. be enough? Concerns that need addressing?
• Once BLA is approved any manufacturing change must be reported as appropriate. Comparability must be demonstrated as appropriate. For a biosimilar, when submitted, the specification limits are based on reference product data, manufacturing experience, clinical experience.
  – If specification changes are proposed would you do so within the reference product specifications, not outside?
    • This is the thought, yes
    • There is little visibility to originator specifications. Therefore, specifications are set based on manufacturing experience of the biosimilar
    • General knowledge should be available of reference product specifications. Similar to an innovator, specification changes have to be reflective of what is known about process, and clinical relevance.
    • There is not enough clinical experience for a biosimilar, so adherence to reference product quality range should be tied in with manufacturing experience.
  – Is there any extra analytical burden when demonstrating comparability for biosimilars?
    • Thorough understanding of your product is necessary.
    • Until 2020, submissions for biosimilars operate in a “grey” regulatory space.
  – How do you demonstrate bioequivalence when structural similarity is not quite there? For example for ADCs, if analytical profile is not equivalent?
    • A clinical trial would likely be needed
  – Is the expectation from the regulatory agency that any post approval change is treated like any change for an innovator molecule?
    • Interchangeability vs. Biosimilarity? There is draft guidance on interchangeability, which addresses post-approval changes that may impact design of drug delivery system. There is little experience with post-approval changes for products approved as biosimilars, as there are no major manufacturing supplements for approved molecule biosimilars.
    • Always follow comparability principles.

2) Specification changes for potency methods
  – Is there expectation to have multiple potency assays to demonstrate similarity for release/stability specifications based on the MOA of the indication if reference product has multiple MOAs?
    • It is possible. Biosimilar product is expected to have adequate control specifications to ensure the future product quality not drifting away from the established quality ranges (e.g. Tier 2 attributes) of reference product.
    • It is possible to have slightly different product profiles

3) Discussion on the possibility of drift of quality attributes if innovator and biosimilar company make changes overtime post-approval
  – It may be a concern. Control of drift is expected. The reference standard should be anchored to the reference product.
- Makes sense to have specifications within clinically relevant range.
- Likely biosimilars have a tighter range if based solely on manufacturing process consistency than reference product.
- There are some countries that may expect you to go back and demonstrate similarity post-approval recognizing that a standard/guidance for how to deal with post-approval changes for biosimilars has not been globally established.

4) Discussion on harmonization of guidelines
- How soon do we foresee other countries are coming on board?
  - International policy is more of an ICH question.
- How big of a difference has industry experienced between FDA review and other countries?
  - EMA and FDA have defined standards with common philosophy. Concern with interacting with FDA is that FDA does not offer statistical guidance for post-approval demonstration of comparability. For example, if the originator changed process and statistical equivalence is no longer achievable for the biosimilar. They have been very vigilant in monitoring originator, but no connection is made to impact to biosimilar.
  - If the change is Tier 1, there should be an assessment of how meaningful those data points are with regard to the MOA and clinical relevance. Should not “cherry pick” data. Focus on relevance. Biosimilar company should not be penalized for having tighter data.

5) Hypothetical case: Process change – impurity profile changes in some way, are they OK? Or of impurity profile from biosimilar is better
- Should be evaluated case by case.
- If post-change biosimilar shows a “cleaner” impurity profile, but still analytically comparable? Where the cut-off would be drawn to determine if no additional clinical work is needed?

6) Some of the CQAs are measured with compendial methods (very old methods) and the biosimilar company may have better/more sensitive methods. With better or more sensitive methods, there is increased likelihood that additional impurities may be detected.

7) Are regulators concerned with coming up with “better”/different delivery systems post-approval?
- According to the draft FDA guidance on interchangeability, an improved design is acceptable provided that it’s justified and interchangeability claim is not compromised.
- Conversely, if originator changes delivery system, is the biosimilar company obligated to change it as well?
  - No.
  - Ambiguity around this may lend itself to originators changing presentations just when a second company is getting ready to submit biosimilar for approval.

8) Interchangeability guideline just came out last week. The foundation is more in clinical nature, with no analytical component. Can this be addressed? Is it too late?
- Interchangeability is not in the scope of this topic, we will defer it to a later appropriate setting for discussion.

9) Have the attendees at the roundtable submitted or have reviewed submissions for post-approval changes (PAC) for biosimilars?
Two representatives of biopharmaceutical industry confirmed they have either submitted PAC with successful approval or are planning to submit a PAC using a protocol.

10) Is the thinking that a company from another country may come to the US for commercialization, since they are more ahead than other countries?

- There are precedents for countries with minimal infrastructure to approve a biosimilar using reciprocity with another country that has approved the medicine.