aam
Association for Accessible Medicines

Biosimilars Council
A Division of the Association for Accessible Medicines

GRx+Biosims™
Generic + Biosimilar Medicines Conference

Post Approval Changes: Best Practices and Strategies

Billie Wiltison
Senior Director, Regulatory Affairs, Vertice Pharma

Post-Approval Changes: Challenges for Industry

- Implementation
  - Managing FDA conversion of filing category (e.g., CBE-0 to a CBE-30)
  - Approval time for a CBE-30 (no goal date)

- Strategy for filing and implementing additional changes to documents in pending supplemental applications
  - Filing only a narrative in the supplement vs the actual document
  - Filing additional changes to the same document – be sure to reference pending supplemental applications impacting the document and when / how those changes will be incorporated in the new version

- Managing complex submissions
  - Multiple changes / documents in one supplemental application – use of a cover letter and reviewer guide
  - Multiple products with similar change – use of a grouped supplement

To get clarity on the challenges for best practices and strategies, questions were created that will facilitate dialogue and discussion....

GRx+Biosims™

FDA Correspondence on Supplemental Applications

- Could the Agency clarify the statement found in CBE-0 correspondence that states ‘filing determination will not be granted for 30 days’? Is the Agency’s expectation that the change is not implemented for 30 days even though it was filed as a CBE-0?
- When notification is received that a CBE-0 has been converted to a CBE-30, typically it is a notification only – it does not indicate any action that is needed based on the company’s implementation of the change upon filing. What is the Agency’s expectation around product already manufactured and distributed with this change?

Scaling up from ANDA approved Batch Size

- In an original ANDA, the company files the same proposed commercial batch size as the ANDA exhibit batches (no scale up). Prior to approval / launch, the batch size is scaled up within 10 x. This type of change would normally qualify as a SUPAC Level 1 change that can be filed in the AR since it is within 10 x of the ANDA batch size. Assumption: Parameters are adjusted based on the batch size increase, bigger version of same equipment, but no other process or parameter changes. Is it acceptable to file the scaled up batch record in the first post-approval AR (and use this MBR for launch), or is the expectation that validation / launch will be done on the ANDA approved commercial batch size?
- What is the Agency's expectation for scale up beyond 10 X – the SUPAC IR Q&A (which supersedes the recommendations in SUPAC-IR Guidance) states that all changes of nonprotein drug product manufacturing batches can be AR – does this also represent the Agency's thinking for ER products (that do not have a Q&A), or other dosage forms (such as liquids) that don't have a SUPAC guidance?

PAS for Additional Strengths

- ANDA stability testing Q&A (II.A.Q1.A1) states that the stability guidance ‘does not apply to post-approval changes’. Other guidances use of the term ‘ANDA’ is specified to include ANDAs and new strength PAS submissions. Some companies have filed (and received approval) for an additional strength with 1 batch and 3 months acc. and long term data. Other companies are filing 3 batches with 6 months acc. and long term data. What is the Agency’s expectation on the data required to support an additional strength PAS?

Supplements for DMF Updates

- Companies are filing references to an updated DMF for a process change, or spec change for example (unrelated to facilities), and are receiving deficiencies based on hidden facilities in the DMF. What is the Agency's expectation on filing post-approval correspondence for 'new' requirements such as including these facilities in the ANDA – should a post-approval submission be filed specific to hidden facilities (not just when another, non-related change to the DMF is being submitted) and if so, what filing would be required as this isn't a 'new' facility, it has always been referenced in the DMF (just not in the ANDA)?
- What does the Agency recommend if the DMF holder refuses to share the facilities used / referenced in their DMF?

Submissions for New Drug Product Manufacturing Sites

- When a company has a new manufacturing site (not previously inspected by FDA) and therefore requires a PAS per the Guidance, is it the Agency's expectation that a PAS is filed for each solid oral dosage form – specifically, could a PAS be filed for one solid oral dosage form (for example an ER tablet) and subsequent solid oral dosage forms (for example an IR tablet, ER capsule, or IR capsule) could be filed in a CBE-30, or would a PAS be required for each solid oral dosage form (e.g., a PAS would be required for an IR Capsule, an ER Capsule, an IR Tablet, and an ER Tablet)?
- What about the same scenario for a new packaging site?

ANDA Withdraw

- When an ANDA has been withdrawn (correspondence submitted), but the withdraw notice has not yet posted in the Federal Register, what is the Agency's expectations with respect to filing ARs, PADERs, and RLD Safety Labeling Updates?
- Can an applicant request that an ANDA be withdrawn when the product is not currently marketed, but stability is ongoing for (previous) annual lots, or is the Agency's expectation that all annual lots have been tested through shelf life and the data filed in the AR prior to requesting that the ANDA be withdrawn?
- If an ANDA is discontinued (not currently marketed) and the only approved drug substance (or drug product) manufacturing site is closing (i.e., the only approved drug substance or drug product manufacturer must be withdrawn from the ANDA as the site will not exist, and therefore not self ID or pay GDUFA fee), will the Agency request that the applicant withdraw the ANDA as there is no viable drug substance (or drug product) manufacturer, or is this acceptable that there is not a viable site since the product is not currently marketed?

Planned Significant Changes Impacting Multiple Products

- When / how should the Agency be notified of significant changes that will impact multiple products / ANDAs such as a new facility or closing of a facility?