Considerations for Post-Approval Changes to Complex Generic Drug Products

Darby Kozak

Deputy Division Director

Division of Therapeutic Performance/ ORS / OGD / CDER / FDA

AAM GRx + Biosims 2022 WorkShop
November 8, 2022

Disclaimer

This presentation reflects the views of the author and should not be construed to represent FDA's views or policies

Overview

- What are complex generic drug products and Generic Drug User Fee Amendments (GDUFA) commitments related to post-approval changes.
- Leveraging GDUFA research and the product-specific guidance (PSG) program to support post-approval changes.
- Example of studies conducted to support post-approval change in the delivery device for a complex nasal spray.
- Potential post-approval changes for complex products that may warrant additional discussion, collaboration, and research.

What are Complex Drug Products

- GDUFA II Commitment Letter introduced what are complex products for generic drug development.
- Recently posted MAPP 5240.10 provides details and examples of how products are classified as complex. These products generally includes one or more of the following five features:

1. **A complex active ingredient**
   Heterogenous mixtures of different components (e.g., conjugated estrogen, omega-3 acid ethyl esters) or molecular weights (e.g., colesevelam hydrochloride, pentosan polysulfate sodium)
2. **A complex route of delivery**
   Locally acting product (e.g., topical dermatological, local-GI)
3. **A complex dosage form or formulation**
   Formulations that have two or more discrete states of matter (e.g., emulsion, suspension, cream); generally, any non-solution products for routes other than oral administration
4. **A complex drug-device combination product**
   Device design may impact drug delivery to the site of action and/or absorption and labeling indicates that users should be trained by a healthcare provider
5. **"[C]omplexity or uncertainty concerning the approval pathway or [a] possible alternative approach [that] would benefit from early scientific engagement"**

Complex Drug Products and GDUFA Research

- Complexity is drug product specific, but the therapeutic performance of a complex drug product is typically expected to be dependent on the physicochemical properties of the drug product (e.g., formulation and critical quality attributes).
- Therefore, changes to the formulation, manufacturing process, manufacturing site, and/or delivery device warrant appropriate information to support that the proposed change maintains a bioequivalent product.
- GDUFA Research Program provides FDA with dedicated funds to address knowledge gaps to facilitate the development and approval of therapeutically equivalent generic drug products.
  - A key focus on this research is the development of bioequivalence approaches for complex generic drug products.
  - Research priorities are set annually based on public feedback and the next GDUFA Science public workshop is spring of 2023. Check GDUFA Research and Science webpage for updates.

GDUFA Research and PSGs

- PSGs outline FDA's current thinking on the studies and information that are recommended to demonstrate a proposed generic drug product is therapeutically equivalent to a specific Reference Listed Drug (RLD).
- Although focused on the development and approval of new/original abbreviated new drug applications (ANDAs), PSG recommendations may also serve as a starting point on the type of information appropriate to support a post-approval change.
- A PSG may include more than one option to demonstrate bioequivalence. In these instances, an applicant can consider which option or components of the option are appropriate to support the post-approval change.
    - FDA's recent guidance, *Physicochemical and Structural (Q3) Characterization of Topical Drug Products Submitted in ANDAs* (October 2022), outline the current thinking on in vitro characterization approaches to support a demonstration of bioequivalence.

Changes to an Approved NDA or ANDA (April 2004)

- Section 506A of the FD&C Act and § 314.70 of FDA regulations provide for the following reporting categories of changes to an approved application:

1. **Major Change:** a change that has a substantial potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product. A major change requires the submission of a PAS and approval by FDA before distribution of the drug product made using the change.
    - Performance goals for assessing and acting on PASs have not changed from the GDUFA II Commitment Letter to the GDUFA III Commitment Letter (e.g., 6 months of submission date of a standard PAS if preapproval inspection not required, 10 months if preapproval inspection is required).
2. **Moderate Change:** a change that has a moderate potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product. Depending on the nature of the change, one of the following two types of supplements must be submitted to FDA for a moderate change: a CBE-30 or CBE-0 supplement.
3. **Minor Change:** a change that has minimal potential to have an adverse effect on the identity, strength, quality, purity, or potency of a drug product as these factors may relate to the safety or effectiveness of the drug product. The applicant must describe minor changes in its next annual report.

Example of Post-Approval Change to a Complex Drug Product: Nasal Spray Suspension

- Changes in bottle dimension, actuator skirt length, dip tube length, and pump material.
- Typically, PSGs for nasal spray suspension products recommend both in vivo and in vitro studies to demonstrate bioequivalence.
- Given the proposed changes were to the delivery device component and did not include changes to the formulation, approval was based on the in vitro studies (i.e., single actuation content, droplet size distribution, and spray pattern) recommended in the PSG. These in vitro studies support equivalent drug delivery characteristics and so additional in vivo studies were not warranted.

Post-Approval Study Tips

- Specify changes
  - Specify the details of the changes, irrespective of the degree of the changes
- Provide justification for why the studies conducted support the changes
- FDA recommends that the comparator for ANDA post-approval changes be the reference listed drug/reference standard*
- Provide relevant documents just as those for pivotal BE studies, for example:
  - Summary tables (in both .doc and .pdf formats)
  - Study protocols and reports
  - Standard operating procedure(s) (SOPs)
  - Certificate of analysis (s) (COAs) for test and reference standard product batches used
  - Study datasets (in SAS .xpt format)

* In some instance testing is against the pre-change product when specified in guidance (e.g., per SUPAC guidance).

Comparability Protocols for Post-approval Changes to the CMC Information in an NDA, ANDA, or BLA (Oct 2022)

- An approved comparability protocol (CP) is an agreed-upon plan to implement specified change(s), and in many cases, a justification to report the change(s) in a reduced reporting category (e.g., a CBE-30 rather than PAS or via annual report rather than CBE-0).
- A CP may be considered suitable for changes in:
  - Manufacturing process scale (scale-up, scale-down, scale-out), where submission of a supplement would ordinarily be needed
  - Formulation or manufacturing that can be evaluated using in vitro studies without the need for an in vivo bioequivalence study.
  - Container closure system provided potential effects of the interchangeability of container closure system components on product quality are addressed.
  - Cross-referenced DMF (e.g., addition of a supplier of a drug substance used in an FDA-approved drug product, a change in an excipient supplier, a change in the supplier of a container and/or closure) provided the CP include the tests and studies to be performed and the acceptance criteria to be achieved to demonstrate the suitability of the material supplied by the DMF holder.
- A CP may NOT be considered suitable for changes that:
  - Need to be supported by an in vivo bioequivalence study
  - Give rise to new impurities that would need to be supported by a toxicology study and/or an in vivo immunogenicity study

Potential Post-Approval Changes of Interest for Further Discussion and Research

- Types of post-approval changes to transdermal, long-acting injectables, inhalation drug products, and other drug-device combination products that may warrant in vitro and/or in vivo studies.
- Information to support the immunogenicity risk assessment for post-approval changes of peptide and oligo products.
  - Comparative impurity profiles, innate and/or adaptative immunogenicity assays, number of lots to test and testing at beginning and end of shelf-life.
- Switch from hydrofluoroalkane (e.g., 1,1,1,2-tetrafluoroethane) to low global warming propellants for orally inhaled drug products.
  - Types of studies that may be needed to support propellant change and appropriate regulatory pathway e.g., 505(b)(1), 505(b)(2), ANDA, or PAS.

Summary

- Drug products may have multiple aspects of complexity that need to be considered when developing appropriate studies to support a post-approval change to the product.
  - In vitro studies demonstrating equivalence of the spray properties were conducted to support post-approval change in the delivery device for a complex nasal spray
- The GDUFA research program and PSGs may be leveraged when considering what studies may be appropriate to support a post-approval change.
- Post-approval changes for complex products that may warrant additional discussion, collaboration, and research. Controlled correspondence may be used for application specific feedback and via FDA held public workshops for feedback on priority areas where research or further guidance may be needed.

References

- MAPP 5240.10 *Classifying Approved New Drug Products and Drug-device Combination Products as Complex Products for Generic Drug Development Purposes*
- GDUFA II Commitment Letter *GDUFA Reauthorization Performance Goals And Program Enhancements Fiscal Years 2018-2022*
- FDA's GDUFA Science & Research Webpage
  - FY23 Generic Drug Science and Research Initiatives Public Workshop
- FDA's guidance for industry*:*
  - *Changes to an Approved NDA or ANDA* (April 2004)
  - *Comparability Protocols for Post-approval Changes to the CMC Information in an NDA, ANDA, or BLA* (October 2022)
  - *Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation Nonsterile Semisolid Dosage Forms* (May 1997) - (SUPAC-SS)


FDA
U.S. FOOD & DRUG
ADMINISTRATION