U.S. FOOD & DRUG ADMINISTRATION

FDA-EMA Parallel Scientific Advice Pilot Program for Complex Generic/Hybrid Drug Products

SBIA Webinar—Expanding Generic Drug Access Through International Engagements

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Outline

- Provide an overview of various international engagements to promote harmonization of BE standards for generic drugs
- Describe the scope of FDA-EMA Parallel Scientific Advice (PSA) Pilot Program for Complex Generic/Hybrid Drug Products
- Describe what products are defined as complex products by FDA and as hybrid products by EMA
- Delineate the goals of the PSA pilot program
- Share what FDA has learned through the PSA pilot
- Describe tips for industry to participate in the PSA pilot

International Engagements

- Collaborate and share information
  - **Generic drug cluster**
  - **IPRP working groups**
- Promote harmonization of BE standards
  - **GBHI**
  - **GDG**
  - **ICH**
- Reduce redundancy and promote efficient generic drug development
  - **Parallel Scientific Advice**

GBHI: *The Global Bioequivalence Harmonisation Initiative*
IPRP: *The International Pharmaceutical Regulators Programme*
GDG: *Generic Drug Discussion Group*
ICH: *The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use*
PSA: *Parallel Scientific Advice*
IR: *Immediate Release*
MR: *Modified Release*

Scientific Harmonization of Bioequivalence Standards for Generic Drugs under ICH

- A series of ICH guidelines on standards for demonstrating equivalence (e.g., bioequivalence) for
  - Non-complex dosage forms (e.g., immediate release oral products)
  - More complex dosage forms and products

ICH M13: "BE for immediate-release solid oral dosage forms"

Parallel Scientific Advice (PSA) Program for Complex Generics/Hybrid Products

Launched on **September 15, 2021**

The **Parallel Scientific Advice (PSA)** pilot program between FDA and European Medicines Agency (EMA) established a new PSA process for ***complex* generic drugs (FDA)/hybrid products (EMA)**

- An expansion to the existing PSA programs for new drugs (CDER) and vaccines or gene therapies (CBER)

The PSA pilot program allows for applicants to engage in **concurrent scientific conversation** with both agencies on key issues during the development phase of ***complex generic drug products/hybrid products***

PSA General Principles document

Complex Products (FDA)

Complex active pharmaceutical ingredient (API)	• Any drug product containing a complex API, regardless of administration routes and dosage forms. e.g., Conjugated Estrogen Tablet, Glatiramer Acetate Injection
Complex routes of delivery	• Any non-solution drug product with a local (non-systemic) site of action (e.g., topical, ophthalmic, local gastrointestinal (GI) action) e.g., Cyclosporine Emulsion, Acyclovir Cream
Complex dosage forms/formulations	• Any non-oral complex formulation/dosage form product where there are often two or more discrete states of matter within the formulation e.g., Doxorubicin HCl Liposomes, Leuprolide Acetate for Depot Suspension
Complex drug-device combinations	• Where the drug constituent part is pre-loaded in a product-specific device constituent part or is specifically cross-labeled for use with a specific device, in which the device design affects drug delivery to the site of action and/or absorption e.g., Epinephrine Injection (autoinjector)
Other products	• Any solid oral opioid drug products with FDA approved labeling for that show properties (and thus gaining their labeling) to meaningfully deter drug abuse e.g., Hydrocodone Bitartrate ER Tablet

Lionberger R. Innovation for Generic Drugs: Science and Research Under the Generic Drug User Fee Amendments of 2012, Clinical Pharmacology & Therapeutics (CPT), 2019, Vol.105(4), p.878-885;
GDUFA III Commitment Letter;
MAPP 5240.10: Classifying Approved New Drug Products as Complex Products for Generic Drug Development Purposes (April 2022)

EMA Hybrid Products

- The EMA uses the term “hybrid medicines” for medicines whose authorization depends partly on the results of tests on the reference medicine and partly on new data, some of which can include what FDA defines as complex products
  - Submit through Market Authorization Application (MAA) Article 10 (3) (Hybrid Medicinal Product Application)
    - where the strict definition of ‘generic medicine’ is not met
    - where the bioavailability studies cannot be used to demonstrate bioequivalence
    - where there are changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration of the generic product compared to the reference medicine
- Some complex products under FDA definition can be “generic medicines” in EMA through MAA Article 10 (1) (Generic Medicinal Product Applications) if BE studies are sufficient to support approval
  - For example, long-acting injectable products
  - These products can be under the scope of PSA

https://www.ema.europa.eu/en/documents/presentation/presentation-legal-basis-types-approvals-s-prilla_en.pdf

Why PSA for Complex Generics?

Current challenges:
Some complex products need very substantive, and resource- and patient-intensive studies. To duplicate these cost in both the EU and US systems is non-optimal.

- Increases dialogue between the two agencies
- Optimizes the applicant's global product development program by enabling them to discuss specific questions concurrently with both agencies
- Further provides applicants with a deeper understanding of the basis for regulatory decisions from both agencies
- Drives convergency to help applicants avoid redundant replication of work and unnecessary testing replication or unnecessary diverse testing methodologies
- Shortens the time to drug development and approval

Examples of Good Candidates for PSA Meetings

- Proposals for a single bioequivalence (BE) study that may satisfy both agencies, especially when FDA and EMA have different recommendations in their respective product-specific guidances
- Proposals for scientific approaches with data/information to support the use of a common comparator in BE studies that are acceptable to both agencies
- Proposals to use modeling and simulation to improve efficiency of the development program

What Have We Learned? (1)

The number of applicants who submit generic drug applications to the FDA and the centralized EMA process is limited

- Two PSA meeting requests were granted and have gone through the PSA process
- The PSA program can be an opportunity to expand the number of generic drug applicants that do submit applications to both jurisdictions

Some applicants have expressed concerns that the PSA program would require additional testing beyond what would be expected if the applicant sought individual advice from each regulatory agency

- However, that has not been the experience with the pilot applicants

A learning experience for both regulators and applicants

- Understand differences in process and meeting expectation
- Converge on Science

What Have We Learned? (2)

In general, the pilot provided a unique forum for increased global collaboration, demonstrating long-term potential for both regulators and applicants

- Immediate benefits were more visible to regulators than applicants
- The designed process can be clarified and further improved

Recommendations were made based on program's preliminary assessment

- Procedural clarifications
- Clarity of the timeline and expectations
- Best practices for meeting package preparation and participation

FDA has communicated with EMA to implement key recommendations to further improve the PSA process

Tips for Participation

- Know the Process
- Consider and be aware of the jurisdiction differences
- Define the purpose to optimize trilateral FDA and EMA meeting expectations
- Work closely with project managers along the way

Take Home Messages

- Through the PSA process, generic applicants can gain an understanding of both agencies' recommendations on specific questions regarding the global development of complex generic drugs or hybrid products
- The PSA pilot is ongoing to accept more meeting requests so that areas of improvement can be identified to support future recommendations
- We highly encourage applicants to participate
  - FDA is mostly interested in submissions that have the potential to reduce duplicative studies for complex generic products

https://www.fda.gov/drugs/our-perspective/cders-ogd-and-emas-parallel-scientific-advice-pilot-program-complex-generics-works-increase

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