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

SBIA 2023—Advancing Generic Drug Development: Translating Science to Approval

Day 2, Session VIII: Global Collaboration to Support Efficient Generic Product Development & Regulatory Assessment

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Polling Question #1

Have you heard about the FDA-EMA Parallel Scientific Advice Pilot Program for Complex Generic/Hybrid Drug Products?

A. Yes

B. No

C. Not sure

Polling Question #2

If you are aware of this pilot program, has your company considered participating in this program for Complex Generic/Hybrid Drug Products?

A. Yes

B. No

C. Maybe

D. We do not develop complex generics/hybrid drug products

Objectives

- 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
- Provide highlights of the PSA pilot program and its processes
- Share what FDA has learned through the PSA pilot
- Describe tips for industry to participate in the PSA pilot

Background

- This 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)

- Launched on **September 15, 2021**

- 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 and hybrid products

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?

- 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

Highlights of PSA (1)

- The agencies conduct PSA meetings under the auspices of the confidentiality arrangement between the European Commission, the EMA, and FDA

- Provide a mechanism for EMA and FDA assessors to concurrently exchange with applicants their views on scientific issues during the development of complex generic drug and hybrid products

- Alignment between agencies can lead to more efficient, leaner global development

- Voluntary for applicants

PSA General Principles document

Highlights of PSA (2)

- Candidates for the PSA program include product development programs that may benefit from the PSA process by potential harmonized approaches
  - For example, the applicant may use the PSA program to determine whether a study design(s) might be acceptable to both regulatory agencies.
  - Studies that may benefit from the PSA process include comparative non-clinical and comparative clinical studies involving innovative bioequivalence study designs and the use of methodologies such as modelling and simulation.

- After the PSA process, each agency will retain its individual regulatory decision-making regarding drug development and marketing applications

- Both agencies will strive to provide PSA responses that are convergent or explain differences

- Any EMA fees applicable for scientific advice are unaffected by PSA status

- PSA meetings are not Generic Drug User Fee Amendments (GDUFA) meetings and are not subject to the performance goals for scheduling and conducting GDUFA meetings

PSA General Principles document

PSA Processes (1)

- **The PSA process** is designed to align the process and timeline of the pre-ANDA product development meeting at the FDA **as much as possible** with the process and timeline mandated by EMA Scientific Advice Working Party (SAWP) for their Scientific Advice (SA) process

PSA General Principles document

PSA Processes (2)

Stage 1: PSA Meeting Requests (14 days)

-Applicant submits one single "Request for PSA" letter (justification letter) to both emainternational@ema.europa.eu at EMA and preANDAHelp@fda.hhs.gov at FDA

-No full package is needed

Stage 2: Meeting Preparation and Conduct (~120 days)

~Day -30*: If the meeting request is accepted, **draft full package submission to EMA for validation review (optional; FDA will get a copy)**

Day 1: Full package is submitted

~Day 90: Bilateral meeting between EMA and FDA**

~Day 120: Trilateral meeting between applicant, EMA and FDA**

Stage 3: Post-Meeting Agency Communication (30 days)

30 days after the trilateral meeting: EMA CHMP final advice letter and FDA meeting minutes will be independently sent to applicants by EMA and FDA, respectively

CHMP: The Committee for Medicinal Products for Human Use

*Timeline varies; Applicant works with EMA

** Meeting dates will be determined by the annual SAWP meeting schedule

Comparison Between PSA and PDEV Meetings

	Parallel Scientific Advice (PSA)	Product Development (PDEV)
Eligible Products	Complex/Hybrid Products*	Complex**
When to Request a Meeting	Seek advice from both FDA and EMA on a global development program	Generally, no PSG, or new alternative BE methods different from PSG recommendation
How to Request a Meeting	A single request to two email boxes: emainternational@ema.europa.eu (EMA) and preANDAHelp@fda.hhs.gov (FDA)	Send request through NexGen Portal
Grant/Deny Decision Timeline	14 days to determine if accept full package	14 days
Days to Conduct Meeting	~120 days from receiving the full package***	120 days from meeting being granted
Participants at the Meeting	FDA, EMA and Applicant	FDA and Applicant
Format of the Meeting	Teleconference with video option (Videoconference)	In Person face-to-face or videoconference
Meeting Length	90 min	60 min

*Some complex products under U.S. FDA definition may be generic products under EMA. These products may also be eligible for PSA

** A PDEV meeting may be granted for a non-complex generic product

***The time between meeting request is accepted and full package submission could vary

PSG: product-specific guidance; BE: bioequivalence

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 applications

What have We Learned? (2)

- A learning experience for both regulators and applicants
  - Understand differences in process and meeting expectation
  - Converge on Science

- In general, the pilot was implemented as intended, demonstrating long-term potential
  - Immediate benefits were more visible to regulators than applicants
  - The designed process can be clarified and further improved

What have We Learned? (3)

- Recommendations 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 and implemented key recommendations to further improve the 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

Challenge Question #1

- The parallel scientific advice (PSA) meeting is part of GDUFA meetings and will follow GDFUA meeting process and timeline

A. True

B. False

Challenge Question #2

- What are the following products that may be eligible for the PSA pilot? Select all that apply

A. Long-acting injectable products

B. Immediate-release oral products

C. Modified-release oral products

D. Orally inhaled products

Take Home Messages

- Through the PSA process, ANDA 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

Resources

- FDA-EMA Parallel Scientific Advice Pilot Program for Complex Generic/Hybrid Products | FDA
- Global Generic Drug Affairs | FDA
- Questions about the program may be directed to preANDAHelp@fda.hhs.gov

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