

15 September 2021

PILOT PROGRAM: EMA-FDA PARALLEL SCIENTIFIC ADVICE FOR HYBRID/COMPLEX GENERIC PRODUCTS - GENERAL PRINCIPLES

The European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services have established a pilot program to provide parallel scientific advice (PSA) to applicants of marketing authorization applications (MAAs) for hybrid products (EMA) and abbreviated new drug applications (ANDAs) for complex generic drug products, hereafter referred to as “complex products” (FDA).¹ The goal of the PSA program is to provide a mechanism for EMA and FDA to concurrently consider and jointly exchange with applicants the agencies’ views on scientific questions during the development phase of hybrid/complex generic products. Such interactions are expected to increase dialogue between the two agencies and applicants from the beginning of the lifecycle of a hybrid/complex generic drug product. Successful collaboration may provide applicants with a deeper understanding of the basis of regulatory decisions, optimize product development, and avoid unnecessary replication of studies or unnecessary testing methodologies. The agencies conduct PSA meetings under the auspices of the confidentiality arrangement between the European Commission, the EMA, and FDA.

EMA and FDA have agreed to the following principles for the pilot program. Posting this “General Principles” statement on the websites of both agencies will make the PSA program’s process and goals more transparent and help answer questions about the program. Each agency will post this statement on its website in accordance with its own procedures.

The pilot will begin on September 15th, 2021 and meeting requests will be received until a sufficient number of PSA meetings are held to support the pilot program. As described in detail

¹ While hybrid products (EMA) and complex products (FDA) have different regulatory definitions, the PSA program will be available to those products where EMA and FDA’s definitions overlap. For EMA, complex generics are hybrid applications under Article 10(3) of Directive 2001/83/EC as amended: “In cases where the medicinal product does not fall within the definition of a generic medicinal product as provided in paragraph 2(b) or where the bioequivalence cannot be demonstrated through bioavailability studies or in case of changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration, vis-à-vis the reference medicinal product, the results of the appropriate pre-clinical tests or clinical trials shall be provided.” For FDA’s definition of a *complex product*, see the GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (GDUFA II Commitment Letter or Goals Letter), available at <https://www.fda.gov/media/101052/download>.

below, there are three stages in this pilot PSA meeting process: 1) Stage 1, applicants request a meeting with EMA and FDA; 2) Stage 2, EMA and FDA assess the meeting package, the agencies conduct a preparatory bilateral meeting, and then conduct a trilateral meeting with the applicant; and 3) Stage 3, EMA and FDA communicate written responses to the applicant. During and after conclusion of the pilot, each agency will evaluate the benefits and challenges of the program, including the resources required, and determine next steps.

1. The PSA program is voluntary. To participate in the PSA program, applicants submit requests to EMA and FDA following the process delineated in this document. “Applicant” refers to: (a) a potential marketing authorisation applicant under the marketing authorisation process in the European Union, or (b) a potential applicant of an ANDA that is expected to be submitted to the FDA.
2. The PSA program focuses on sharing information and perspectives. Achieving harmonization and increased convergence are potential benefits of the PSA program. Following a PSA meeting, an applicant will have a clearer understanding of the agencies’ respective regulatory requirements and scientific recommendations regarding the development program discussed. If advice from the two agencies is divergent, the applicant will have a clear understanding of the reasons for divergence.
3. 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.
4. Requests for PSA meetings will be granted based on the workload, availability of staff, and anticipated value to the PSA program. For each request, the agencies will hold one trilateral meeting with the applicant focused on the specific development issue raised. The trilateral meeting will generally be one and a half hours but may be longer based on the number and complexity of questions to be discussed in the meeting.

Stage 1: PSA Meeting Requests

5. Applicants submitting a PSA meeting request should:
 - As a general matter, focus on and develop specific scientific questions involving the development of a hybrid/complex generic product for which the applicant desires to have further scientific input from both EMA and FDA.
 - Submit one single “Request for PSA” letter (justification letter) to both emainternational@ema.europa.eu at EMA and preANDAHelp@fda.hhs.gov at FDA. In the justification letter, provide the following information:

- Pre-assigned ANDA number²
 - Applicant information
 - If the applicant is not based in the U.S., also provide the U.S. agent information; if the applicant is based in the U.S., provide a statement indicating whether the submission is being made by the ANDA applicant or by a U.S. agent on behalf of the ANDA applicant
 - Contact person for the meeting (i.e., the person submitting the meeting request), with their title and affiliation, secure email address, and phone number. This is the person with whom EMA and FDA will communicate about the meeting.
 - Information on previous interactions with EMA, research product identifier (RPI) if already assigned
 - Information on the product in development and the reference listed drug
 - A brief statement of the purpose and objectives of the meeting, including why a discussion with EMA and FDA would be beneficial to the product's development
 - Specific questions for discussion
 - How long it will take the applicant to submit a full meeting package to EMA and FDA if the meeting request is granted
 - An explicit authorization for the agencies' comprehensive exchange of all information relevant to the product, including trade secret information (as defined by U.S. statute). Pursuant to legally established authorities, both agencies will maintain the confidentiality of all such information.
6. A PSA request does not guarantee that the PSA meeting will be granted. For a variety of reasons, one or both agencies may decline to participate in such a meeting.³ If an applicant's request for a PSA meeting is not granted, the applicant is free to pursue a scientific advice procedure with each agency individually, following each agency's normal procedures.⁴ Alternatively, both agencies

² See FDA's website for information on requesting a pre-assigned application number:

<https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/requesting-pre-assigned-application-number>.

³ FDA will generally follow the principles, as relevant, outlined in the Manual of Policies and Procedures (MAPP) 5220.8, titled "Evaluating Requests for and Conducting Product Development and Pre-Submission Pre-ANDA Meetings," available at: <https://www.fda.gov/media/130874/download>.

⁴ For information on submitting controlled correspondence or a pre-ANDA meeting request to FDA, see FDA's guidance for industry, *Controlled Correspondence Related to Generic Drug Development* (Dec. 2020) and *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* (Nov. 2020).

can engage in a “consultative advice.”⁵ In the consultative advice process, a limited number of experts from either side will be invited to participate in the discussions of the other agency. In addition, applicants should not submit the same meeting request through both PSA and FDA’s pre-ANDA program at the same time.

Stage 2: Meeting Preparation and Conduct

7. If both agencies grant the applicant’s PSA request, the applicant will receive an email from each agency, pursuant to each agency’s standard procedures, acknowledging such agreement and indicating the primary contact person at each agency. Applicants should submit a draft meeting package to EMA via the IRIS portal (<https://iris.ema.europa.eu/>)⁶ for validation review and potential revision thirty days prior to submitting the full meeting package (i.e., on “day -30” as described in the Appendix).⁷ Once the meeting package has been validated by EMA, the final full meeting package should be submitted to both the EMA via the IRIS portal and the FDA via preANDAHelp@fda.hhs.gov (i.e., on “day 1” of stage 2 as described in the Appendix). In the full meeting package, the applicant should provide:⁸
 - A brief history of the development program and the status of product development
 - A list of questions for discussion, grouped by topics, as applicable, with each question clearly numbered (e.g., 1, 2, 3 without sub-questions). For each question, there should be a brief explanation of the context and purpose of the question and any supporting rationale or data, as applicable. The package should be organized such that following a summary list of all questions, each question is followed by the corresponding supporting justification, rationale, or data as applicable, followed by the next question.
 - Data to support discussion organized by question. The level of detail should be appropriate to the meeting type requested and the product development stage.
8. Stage 2 of the PSA process generally corresponds to the 120-day timeline for a pre-ANDA meeting at the FDA, which covers the 70-day timeline mandated by EMA Scientific Advice Working Party (SAWP) for

⁵ The Consultative Advice procedure allows applicants to request scientific advice from one regulatory agency and concurrently notify the other regulatory agency of the request. At the invitation of the first agency, the second will participate in the meetings or teleconferences as able. Unlike the PSA process, the second agency will be expected to only engage on top level issues. The review and meeting with the applicant will follow the timelines of the regulatory agency from whom the applicant initially seeks scientific advice. Only the initially contacted regulatory agency will provide written scientific advice in accordance with standard agency meeting procedures.

⁶ See EMA’s website on “How scientific advice works,” available at: <https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance/how-scientific-advice-works>.

⁷ It is recommended that a copy of the draft meeting package also be sent to the FDA at preANDAHelp@fda.hhs.gov for their information.

⁸ For additional information, please see EMA’s recommendations for Scientific Advice requests (https://www.ema.europa.eu/documents/regulatory-procedural-guideline/european-medicines-agency-guidance-applicants-seeking-scientific-advice-protocol-assistance_en.pdf) and FDA’s guidance for industry, *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* (Nov. 2020).

their Scientific Advice process. (The annual SAWP meeting schedule is also accessible via the SAWP web page: <https://www.ema.europa.eu/en/committees/working-parties-other-groups/chmp/scientific-advice-working-party>.) As such, the presently established timelines for the two agencies to conduct scientific meetings may be adjusted to align with either agency's established timelines. The primary contact persons from both agencies will liaise and agree on a schedule for meetings between EMA and FDA (bilateral) and the trilateral meeting with the applicant. The trilateral meeting schedule will then be shared with the applicant (see Appendix for a timeline for the PSA pilot for hybrid/complex generic products).

9. The applicant will participate in a trilateral PSA teleconference with EMA and FDA. In addition, the two agencies will conduct a bilateral pre-teleconference or videoconference prior to the trilateral meeting to further discuss the applicant's questions. The two agencies may conduct a post-teleconference or videoconference after the trilateral meeting with the applicant if needed. If travel is required for an agency representative, it will be at the expense of the agency for which the traveler works. The teleconference or videoconference with the applicant and both agencies will usually be scheduled around 120 days after the applicant submits the full meeting package, in the margins of the EMA SAWP meeting. The EMA List of Issues and FDA's preliminary responses for discussion will be shared approximately 14 days before the trilateral meeting. The designated primary contact for each agency will coordinate final meeting logistics with the applicant.

Stage 3: Post-Meeting Agency Communication

10. After the PSA process, each agency will retain its individual regulatory decision-making regarding drug development and marketing applications. The advice of each agency may still differ after the joint discussion. Each agency will provide the applicant with independent advice on the questions posed during the PSA meeting, according to usual procedures and timelines. Participation in the PSA program will not be construed to ensure any particular action on a marketing application by either agency. However, both agencies will strive to provide PSA responses that are convergent or explain differences.
11. 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.
12. Both agencies remain committed to meeting their individual processes and timeframes. The PSA process should not adversely impact either agency's ability to meet its individual performance expectations. Both agencies commit to be cognizant of the other's domestic performance expectations and to exhibit as much flexibility as possible in scheduling PSA meetings in order to

avoid adversely impacting either agency's ability to meet its domestic performance expectations.



Appendix

Timeline for EMA-FDA PSA Pilot for Hybrid/Complex Generic Products

