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GUIDE

Regulatory Strategy Considerations for Working with the FDA vs. the EMA

As regulatory requirements become increasingly harmonized across the globe, the development and marketing of pharmaceutical products worldwide are also becoming more streamlined. However, global regulations are not one-size-fits-all, and sponsors aiming to market their products in multiple regions should be aware of the current standards and processes they may encounter during the development process. The Food and Drug Administration (FDA) governs the drug and biologic approval process in the United States, while the European Medicines Agency (EMA) serves the European Union (EU) plus Iceland, Norway, and Liechtenstein. As of January 1, 2021, EU pharmaceutical regulations do not apply to the United Kingdom, which formally left the EU in January 2020.[1]

In this guide, we will explore the regulatory strategy considerations sponsors should bear in mind when working with these agencies, with a focus on the development of drug and biologic products. We will compare the approval processes, formal meetings/scientific advice processes, applications for conducting clinical studies, expedited programs, pediatric plans, and labeling for the FDA and the EMA.

Approval process: FDA vs. EMA procedures

The drug approval process represents one of the most obvious differences between U.S. and EU agencies. The FDA oversees all drug approvals in the U.S. via New Drug Applications (NDAs), with approvals for biologic products being approved via Biologics License Applications (BLAs).

In contrast, there are four potential approval pathways for pharmaceuticals in the EU: centralized, decentralized, mutual recognition, or national. While some products have specific requirements dictating which of these pathways is appropriate, in other cases sponsors should think carefully and select the approval procedures most suitable for their products:

- **Centralized Procedure (CP)[2]:** All human medicines derived from biotechnology and other high-tech processes must be evaluated by the EMA via the CP. The same applies to all advanced therapy medicines and medicinal products containing new active substances intended for the treatment of HIV/AIDS, cancer, diabetes, neurodegenerative diseases, auto-immune and other immune dysfunctions, and viral diseases, as well as to all designated orphan medicines intended for the treatment of rare diseases.

  For medicines that do not fall under any of the above-mentioned categories, companies can submit an application to the EMA, provided the medicine is a new active substance, constitutes a significant therapeutic, scientific, or technical innovation, or is in any other respect in the interest of patients at EU level. Also, generics of centrally authorized products and applications for certain medicinal products for pediatric use may be authorized in this way.

The EMA Committee for Medicinal Products for Human Use (CHMP) is made up of representatives from each member state and evaluates Marketing Authorization Applications (MAAs) submitted via the CP. In contrast to the FDA, the EMA does not have the authority to issue approvals. The CHMP evaluates the product's quality, safety, and efficacy and provides an opinion to the European Commission (EC). The EC can then issue an approval decision, which is valid in all EU member states.

- **Decentralized Procedure (DP):** The DP is the most commonly used approval pathway in the EU.[3] The DP applies to all products without a prior marketing authorization in the EU that are not required to use the centralized procedure. An MAA is submitted to a National Competent Authority (NCA) in each member state where the sponsor seeks approval – the Concerned Member States. One member state assumes the position of the Reference Member State and leads the MAA review. An approval decision is then valid across all Concerned Member States to which the application was submitted.

- **Mutual Recognition Procedure (MRP):** The MRP can only be used for products with a prior marketing authorization in at least one member state – initially approved via the national procedure.[4] It relies on the initial marketing authorization by the Concerned Member States' regulatory authorities and is usually granted unless there are indications a product may pose a public health risk.

- **National Procedure:** Since January 1998, the national procedure is strictly limited to products not to be authorized in more than one member state, and to the first phase of the mutual recognition procedure, with an NCA in the chosen member state issuing the initial marketing authorization.[5]

Interactions with Regulatory Agencies: U.S. vs. EU

There are two broad categories of interactions with regulatory authorities – scientific advice procedures and pre-submission meetings – with some overlap between the two. **For scientific advice procedures, the goal is to confirm the adequacy of existing information** to support the next steps in a development program. In addition, the sponsor seeks an agency's agreement on its proposed plans, including clinical and nonclinical studies. **Pre-submission meetings are usually associated with milestone submissions**, such as applications to initiate clinical trials, pediatric investigation plans, orphan designations, scientific advice, or marketing applications. These meetings usually focus on the administrative, regulatory, and technical aspects of a submission and may include discussion of the adequacy of the development program to support the given application.

A sponsor must submit a list of specific questions prior to a meeting with either the U.S. or EU authorities. For EU scientific advice, the sponsor must also provide its position for each question, which is not required for meetings with the FDA.

Another notable difference is in the authorship of the official record for each meeting: The FDA and CHMP provide meeting minutes to serve as an official record, but other regulatory agencies often rely on sponsors to compose the minutes and share them with the agencies. They will then review the minutes, suggest any changes, and may or may not issue confirmation of an official record.

Finally, FDA advice is legally binding; CHMP advice is not legally binding, but deviation from scientific advice without proper justification may result in non-acceptance of a submission for marketing authorization. In Europe, advice from NCAs is not legally binding.

Figure 1. FDA Meeting Types

Meeting Type	Meeting Purpose	Meeting Timing* (from receipt of request)	Meeting Package Due (prior to scheduled date or of WRO** response time)
A	To address a stalled product development plan or an important safety issue	Within 30 calendar days	At the time of meeting request
B	To seek advice in relation to a key milestone (e.g., pre-IND, pre-NDA meetings)	Within 60 calendar days	No later than 30 calendar days prior
B (EOP)	To discuss development progress at EOP2 meetings and certain EOP1 meetings	Within 70 calendar days	No later than 50 calendar days prior
C	To engage in interaction outside of a Type A or Type B meeting, often to seek advice on a specific part of a development program	Within 75 calendar days	No later than 47 calendar days prior

* This meeting timing represents a goal of the FDA, to which the Agency does not always strictly adhere (depending on scheduling between the FDA and sponsor) ** WRO = written response only

Meetings with the FDA

The FDA offers four types of meetings for drugs and biologics: Type A, Type B, Type B (end-of-phase (EOP)), and Type C. (See Figure 2.) All four types are free of charge to the sponsor, in contrast to EU meetings.

CHMP Scientific Advice and National Advice in the EU

Sponsors seeking approval in the EU, regardless of the authorization procedure, can consider meeting with the NCAs in member states to informally discuss aspects of the development program (e.g. novel trial designs or novel endpoints). Meeting with several NCAs allows the sponsor to build a consensus on those aspects before seeking CHMP advice. Additionally, marketing authorization holders engage with NCAs that serve as a rapporteur or co-rapporteur (for CP products) or reference member state (for DP or MRP products), either in a pre-submission meeting prior to MAA, to gain agreement on the development plan, or to discuss upcoming variations to their MAAs. Fees charged vary between NCAs.

Sponsors can also seek scientific advice from the CHMP anytime during development. Discussion topics can include a wide array of issues across quality, nonclinical development, and clinical development. The EMA charges fees for scientific advice meetings depending on the scope of the advice. In 2022, these fees ranged from €46,900 to €94,000, though fee reductions are available for orphan drugs, advanced therapy medicinal products, and small businesses.[6]

Unlike the FDA, which reviews meeting requests and schedules meetings "on-demand," the Scientific Advice Working Party (SAWP) reviews request for scientific advice from the CHMP monthly, 11 times per year, with no meeting in August. Therefore, missing a relevant submission deadline delays the procedure by at least one month. A draft briefing package must be submitted by the sponsor either three weeks, when seeking scientific advice without a preparatory meeting, or approximately seven weeks, when requesting a preparatory meeting, prior to the intended start of the scientific advice procedure. The SAWP reviews the briefing package and decides whether scientific advice can be provided without a discussion meeting, 40 days from the start of the procedure, or whether a 90-minute discussion meeting will be held 60 days from the start of procedure, with final advice being provided 10 days later. In a discussion meeting, a sponsor needs to address requests for clarification of the briefing document, as identified by the reviewers. Responses to the questions from the sponsor are not addressed during this meeting.

Applications for the conduct of clinical studies: INDs vs CTAs

The FDA's Investigational New Drug (IND) application regulations cover all U.S. clinical activities for drugs and biologics. An IND submission serves as a request to start clinical studies, containing a summary of information known about the drug, including nonclinical studies; chemistry, manufacturing and controls (CMC); and a proposed clinical plan. The primary goal of the initial submission is to demonstrate the product's safety for clinical trial participants and to justify the proposed starting dose in humans.

An IND is a living dossier that a sponsor submits before the first clinical study and then expands throughout the clinical program for the given indication, with some INDs accruing upwards of 100 amendments. INDs must contain full study reports of nonclinical and clinical studies, if available. In contrast, full study reports are only submitted for Clinical Trial Applications (CTAs) in the EU upon request by the reviewing authority. The FDA does not charge fees for IND submission or maintenance, another contrast to the process in the EU member states. Fees often apply for CTA submissions both to the National Competent Authority (NCA) of each member state and to relevant Independent Ethics Committees (IECs), which are equivalent to Institutional Review Boards (IRBs) in the U.S.

Applicable clinical trials conducted under an IND or with one or more U.S. sites must be registered at clinicaltrials.gov.[7] On the other hand, clinical trials in the EU are registered at EudraCT.[8] However, the new Clinical Trial Regulation[9] has introduced a major change to the conduct of clinical trials in the EU that addresses several "issues"[10] with the previous system – required registration to each Concerned Member State resulting in multiple submissions for one trial, double submissions to NCAs and IECs, lack of a harmonized dossier, and limited data availability to the public. As of January 31, 2022, a centralized EU portal and database for clinical trials, the Clinical Trials Information System (CTIS), has gone live with the goal of increasing the safety and efficiency of EU trials and increasing the transparency of trial information. Notable changes include a single e-submission to all Concerned Member States, including NCAs and IECs, a joint assessment, and the availability of all information related to the clinical trial.

In the EU, sponsors submit CTAs regardless of the type of approval procedure pursued. There is no centralized process for obtaining approval to conduct a clinical study, so sponsors must submit CTAs to each of the individual member states where the sponsor intends to conduct a clinical trial. Unlike an IND, which covers the entire clinical program for a given product and indication, a new CTA must be submitted for each new trial. The core of many CTAs is the Investigational Medicinal Product Dossier (IMPD), which contains comprehensive CMC information and a high-level summary of a product's nonclinical, and if available, clinical data. In general, reference is made to the Investigator's Brochure for nonclinical and clinical information. An IMPD is brief compared to an IND, as it is revised over time and must be resubmitted with each new CTA. A separate IMPD is required for a comparator or placebo, if applicable.

Expedited programs: Breakthrough therapy vs. PRIME

Several expedited programs/designations exist both in the U.S. and in the EU to aid in the development of medicines for patients with unmet medical needs. In this section, we will focus on breakthrough therapy designation in the U.S. and priority medicines (PRIME) in the EU.

Breakthrough therapy designation[11] is intended for medicines that represent a substantial improvement in safety or effectiveness – as demonstrated by preliminary clinical evidence – over available therapies for the treatment of a serious condition. The FDA offers intensive guidance on development programs that have the designation, beginning as early as Phase 1, as well as enhanced interactions involving senior managers. Products with breakthrough therapy designation may also benefit from priority review, which shortens the NDA or BLA review time from 10 months to six months.[12] Since 2012, 1,057 breakthrough therapy designation requests have been submitted. Of those, 426 requests were granted and 631 denied or withdrawn. If one assumes that withdrawn applications were not deemed approvable by the applicants, the historical approval rate is about 40%. To date, 247 breakthrough-designated drugs have been approved for marketing in the US.[13,14]

The PRIME scheme[15] was launched by the EMA in 2016 to provide increased support for the development of medicines that target an unmet medical need. PRIME offers sponsors enhanced interactions and early communication with the EMA, with the goal of optimizing development and accelerating the evaluation of a product in order to provide benefit to patients as soon as possible. Medicines that offer a major therapeutic benefit over existing therapies or that benefit patients without treatment options are considered for PRIME based on early clinical data. PRIME medicines may also be eligible for accelerated assessment,[16] a counterpart of priority review by the FDA, which reduces the review time of a marketing authorization application by the EMA from 210 days to 150 days. Between 2016 and June 2022,[15] 399 PRIME applications were submitted to EMA.[8] Of those, 25% have been granted, 71% denied, 3% determined to be out of scope, and 1% withdrawn. Of the applicants, 54% were small- or medium-sized enterprises, 1% academic, and 45% other. Most applications (116) were within the oncology therapeutic area.

Pediatric plans: PSPs vs. PIPs

In the U.S., the Pediatric Research Equity Act (PREA)[17] requires sponsors to conduct pediatric studies of certain drugs or biologics – including an age-appropriate formulation – with the goal of obtaining pediatric labeling for the product. PREA instituted a requirement for pediatric study plans (PSPs),[18] which must be submitted no more than 60 days after an End of Phase 2 (EOP2) meeting, or at least 210 days prior to NDA submission if no EOP2 meeting is held. The FDA may defer the requirements or grant partial or full waivers[19] of studies in certain age groups based on low or no occurrence of a specific condition in pediatrics.

In the EU, pediatric investigation plans (PIPs)[20] are analogous to PSPs, but the submission timing is different. A PIP must be submitted to the EMA after Phase 1 pharmacokinetic studies and before Phase 3 pivotal studies. As with the FDA, the EMA may grant partial or full waivers of studies as well as deferrals. Once authorization is obtained in all Member States and study results are included in the product information, even when negative, the medicine is eligible for a six-month supplementary protection certificate (SPC) extension. For orphan-designated medicinal products, the 10-year period of market exclusivity is extended to 12 years.[21]

Labeling: PI vs. SmPC

Labeling information for prescription products approved in the U.S. can be found in the Prescribing Information (PI) and accessed in its most up-to-date form at Drugs@FDA.[22] Labeling information for products approved in the EU is located in the Summary of Product Characteristics (SmPC), accessible via on the EMA website.[23]

As a full-service global regulatory partner, Premier Consulting can help you craft a time- and cost-efficient development strategy that enables you to attain approval in both the U.S. and the EU. Contact us to find out how we can support your program.

References

1. European Medicines Agency. Brexit: the United Kingdom's withdrawal from the European Union. https://www.ema.europa.eu/en/about-us/history-ema/brexit-united-kingdoms-withdrawal-european-union.
2. European Medicines Agency. Authorization of medicines. https://www.ema.europa.eu/en/about-us/what-we-do/authorisation-medicines.
3. Science Direct. Drugs and Devices: Comparison of European and U.S. Approval Processes. https://www.sciencedirect.com/science/article/pii/S2452302X16300638.
4. European Commission. Volume 21, Procedures for marketing authorisation; Chapter 2, Mutual Recognition. https://ec.europa.eu/health/system/files/2016-11/vol2a_chap2_2007-02_en_0.pdf.
5. European Commission. Authorisation procedures – National authorisation procedures. https://ec.europa.eu/health/medicinal-products/legal-framework-governing-medicinal-products-human-use-eu/authorisation-procedures-national-authorisation-procedures_en.
6. European Medicines Agency. Fees payable to the European Medicines Agency. https://www.ema.europa.eu/en/human-regulatory/overview/fees-payable-european-medicines-agency.
7. Clinicaltrials.gov. FDAAA 801 and the Final Rule. Available at: https://clinicaltrials.gov/ct2/manage-recs/fdaaa.
8. EudraCT. Available at: https://eudract.ema.europa.eu/.
9. European Medicines Agency, Clinical Trials Regulation. Available at: https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/ clinical-trials-regulation.
10. European Medicines Agency, Clinical Trials Regulation (EC) No. 536/2014. Available at: https://www.ema.europa.eu/en/documents/presentation/ presentation-key-features-objectives-regulation-eu-no-536/2014-laura-pioppo_en.pdf.
11. U.S. Food & Drug Administration, Breakthrough Therapy. Available at: https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval- priority-review/breakthrough-therapy.
12. U.S. Food & Drug Administration, Priority Review. Available at: https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority- review/priority-review.
13. U.S. Food and Drug Administration. CDER breakthrough therapy designation requests received by fiscal year [table]. Data as of 31 December 2021. https://www.fda.gov/media/95292/download.
14. U.S. Food and Drug Administration. CDER breakthrough therapy designation requests received by fiscal year [table]. Data as of 31 March 2022. https://www.fda. gov/media/95286/download.
15. European Medicines Agency, PRIME: priority medicines. Available at: https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines.
16. European Medicines Agency, Accelerated assessment. Available at: https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/accelerated-assessment.

17. U.S. Food & Drug Administration, Pediatric Research Equity Act, PREA. Available at: https://www.fda.gov/drugs/development-resources/pediatric-research- equity-act-prea.
18. U.S. Food & Drug Administration, Pediatric Development of the Drug or Biological Product. Available at: https://www.fda.gov/media/84944/download.
19. U.S. Food & Drug Administration, Adult-related conditions that qualify for a waiver because they rarely or never occur in pediatrics. Available at: https://www.fda.gov/media/101440/download.
20. European Medicines Agency, Paediatric investigation plans. Available at: https://www.ema.europa.eu/en/human-regulatory/research-development/paediatric-medicines/paediatric-investigation-plans.
21. European Medicines Agency, Better medicines for children. Available at: https://www.ema.europa.eu/documents/leaflet/better-medicines-children_en.pdf.
22. U.S. Food & Drug Administration, FDA-Approved Drugs. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm.
23. European Medicines Agency, European public assessment reports. Available at: https://www.ema.europa.eu/en/medicines/field_ema_web_categories%253Aname_field/Human/ema_group_types/ema_medicine.

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