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**: The centralized procedure2 for EMA approval is required for certain types of products, including treatments for HIV/AIDS, cancer, diabetes, neurodegenerative diseases, autoimmune diseases, and viral diseases, as well as advanced-therapy medicines – such as gene therapies – and orphan drugs. The EMA Committee for Medicinal Products for Human Use (CHMP) is made up of representatives from every member state and evaluates Marketing Authorization Applications (MAAs) submitted via the centralized procedure. 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: The decentralized procedure is the most commonly used approval pathway in the EU. The decentralized procedure 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: The mutual recognition procedure can only be used for products with a prior marketing authorization in at least one member state – initially approved via the national procedure. 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.

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

There are two broad categories of meetings with regulatory authorities – scientific advice meetings and pre-submission meetings – with some overlap between the two. In scientific advice meetings, 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 or marketing applications. These meetings usually focus on the administrative, regulatory, and technical aspects of a submission, while including 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 meetings, 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 provides 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 issue confirmation of an official record.

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. All four types are free of charge to the sponsor, in contrast to EU meetings.
Meetings with the EMA/National Competent Authorities

Sponsors seeking approval in the EU through the centralized procedure should consider meeting with the NCAs in member states, as they provide experts to serve on the EMA’s scientific committees. Meeting with several NCAs prior to submitting an application allows the sponsor to build a consensus on the proposed development program to present to the EMA. The most relevant NCAs are those with experts who are likely to serve as a rapporteur or co-rapporteur for the product evaluation. Fees charged vary between NCAs.

Sponsors whose products qualify for the centralized procedure can also seek scientific advice from the EMA 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. As of August 2021, these fees ranged from €44,400 to €89,000, or about $52,500 to $105,300, though fee reductions are available for orphan drugs and small businesses.  

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Unlike the FDA, which reviews meeting requests and schedules meetings “on-demand,” the Scientific Advice Working Party (SAWP) reviews requests 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 letter of intent, analogous to an FDA meeting request, and briefing package must be submitted by the sponsor either three weeks, when seeking scientific advice without a meeting, or approximately seven weeks, when requesting a pre-submission 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 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.

Most pharmaceutical products in the EU are approved through the decentralized and mutual recognition procedures not overseen by the EMA. Meetings with NCAs in the Reference and Concerned Member States can be crucial to gaining agreement with the agencies on the development program and achieving marketing authorization.

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 Authorizations (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. On the other hand, at the time of writing, September 2021, clinical trials in the EU are registered at EudraCT. However, a new Clinical Trial Regulation introduces a major change to the conduct of clinical trials in the EU that addresses several “issues” with the current 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. On January 31, 2022, a centralized EU portal and database for clinical trials, the Clinical Trials Information System (CTIS), will go 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, as opposed to submitting a single application to the EMA. 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), a comprehensive, high-level summary of a product’s details that
contains overviews of CMC, nonclinical, and if available, clinical data. 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 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. When the designation is granted, the FDA offers intensive guidance on the drug development program, 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. Between 2012 and 2020, 190 medicines received breakthrough therapy designation.

The PRIME scheme 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, 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 2021, 93 medicines – 25 percent of all applications – were granted PRIME eligibility.

**Pediatric plans: PSPs vs. PIPs**

In the U.S., the Pediatric Research Equity Act (PREA) 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), 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 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) are analogous to PSPs; however, the submission timing for a PIP is different. A PIP must be submitted to the EMA after Phase 1 pharmacokinetic studies and before Phase 3 studies. As with the FDA, the EMA may grant partial or full waivers of studies as well as deferrals.

**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. Labeling information for products approved in the EU is located in the Summary of Product Characteristics (SmPC), accessible via the EPAR database.

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.
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About Premier Consulting

Premier Consulting is a strategic product development and global regulatory consulting company dedicated to helping biotech innovators transform their life-changing ideas and breakthrough science into new medical treatments.

Our end-to-end solutions in strategy, regulatory, nonclinical, clinical, CMC, quality, and commercial help sponsors build and execute development plans that meet regulatory requirements and deliver results for sponsors and the patients they serve.

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