

# Drug Review Differences across the United States and the European Union

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Given the globalization of the pharmaceutical industry, harmonizing the drug regulatory environment of the United States (US) and European Union (EU) is becoming increasingly important to accelerate the development of new therapeutics. These regulatory systems are the most rigorous in the world, and together they affect approximately 49% of the global market share [1]. In the US, the Food and Drug Administration (FDA) supervises the drug review process, whereas in the EU this is overseen a coalition of federal organizations that include the European Medicines Agency (EMA), the European Commission, and the national authorities of the EU member states.

The beginning of the FDA dates back to 1906, when the Food and Drug Act empowered the US Department of Agriculture Bureau of Chemistry to regulate pharmaceutical marketing. Branding abuses and public awareness of the dangers of unregulated drugs triggered the passing of multiple amendments to the Food and Drug Act, expanding the regulatory authority of the Bureau, which came to be known as the FDA in 1930. Today, the FDA is a centralized federal agency that reviews and regulates biomedical products and supervises the associated clinical trials, marketing approval, and risk management processes.

Before 1995, drug regulation in the EU was controlled by 15 National Regulatory Authorities representing the respective member states. Thus, to commercialize a drug in the EU, a company had to submit an application to each regulatory authority, a process that often led to different outcomes. In 1995, the EU formed the EMA with the intent to centralize the work of these regulatory bodies and send recommendations to the European Commission [2].

## **Operational Similarities and Differences**

Overall, the FDA and EMA share the same objectives: 1) promote public health, 2) assess the safety and efficacy of therapeutic products, and 3) collaborate with experts to enhance product development. Both organizations mandate preclinical testing, three phases of clinical trials, and a final approval procedure as part of the drug development process. In the US, however, clinical trials and market approval are conducted under the FDA supervision and no authorizations can be obtained at the state level [1]. In the EU, clinical trials are initiated by a member state and market authorization may follow a centralized, decentralized, or a mutual recognition pathway. The centralized pathway allows a candidate drug to be reviewed by the EMA and recommended to the European Commission for final approval. This pathway is mandatory for therapeutics treating specific conditions, such as cancer, HIV/ AIDS, diabetes, and rare diseases. In the decentralized procedure, applications for market authorization by the European Commission can be simultaneously requested by each member state. In the mutual recognition procedure, a drug is first evaluated by a single member state and the assessment may be used to obtain market authorization in another member state. This process is common for the approval of generic pharmaceuticals.

Another difference in drug evaluation process is the metrics adopted for measuring drug efficacy. While both the FDA and the EMA recognize the importance of patient-reported outcomes, the EMA focuses on global assessments of patient-reported quality of life, whereas the FDA focuses on symptom-specific measures and requires early planning and cooperation with patient groups to determine the most important symptom concerns [3].

Market approval in the EU is further complicated by additional regulations adopted by some of the member states that ultimately determine which drug can actually be marketed in that specific state. For example, a drug approved by the EMA also needs approval from the Medicines and Healthcare Products Regulatory Agency in order to be marketed in the United Kingdom. In addition, the National Institute for Health and Care Excellence has to assess potential cost concerns to determine whether the same drug can be purchased by the National Health Service for patient use [3]. Finally, the individual EU member states control sales and promotional activities of all pharmaceuticals [4]. Consequently, the national regulatory authorities are responsible for regulating pharmaceutical advertising, which is instead less restrictive in the United States.

One of the primary issues affecting drug development and approval in the international market is the cost associated with the requirements for additional unanticipated trials, which is often prohibitive for small pharmaceutical companies and can drive up the price of the drug for the consumer. Significant delays in the review process can reduce the profitable use of a patent and unnecessarily limit treatment options for patients with terminal or rapidly progressing illnesses. For example, the centralized market authorization in the EU, which involves multiple regulatory entities (EMA, European Commission, and members states), results in an approval time for oncology therapeutics that is on average twice as long as in the US [5].

Despite the submission of identical clinical data supporting the same drug, the EMA and FDA can come to different evaluations and conclusions. Between 1995 and 2008, 20% of oncological pharmaceuticals were approved by either the FDA or the EMA, but not both, and 28% of approved drugs had significant variations in the label wording [3]. Likewise, the review of existing drugs can produce different restrictive actions. For example, in 1999 and 2000, the EMA issued several Product Safety Announcements on Orlaam, an alternative to methadone for the treatment of opiate addiction, due to concerns for cardiac complications. Subsequent studies linking Orlaam to cardiac arrhythmia led the EMA to withdraw the drug from the EU market in 2001. By contrast, the FDA maintained the drug on the US market, choosing instead to issue labeling revisions. Eventually, the manufacturer voluntarily withdrew Orlaam in 2003 when the sales of the drug fell dramatically due to the FDA-imposed warnings [6].

Discrepancies in the categorization of products for review also present a hurdle. The FDA and EMA have different standards for labeling

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products as drugs or cosmetics, resulting in inconsistent availability to the consumer. Indeed, eight sunscreen ingredients approved for use in Europe have been languishing under the FDA review for more than ten years [7]. In 2014, pressured by manufacturers and advocates claiming that the sunscreen ingredients provided appropriate protection against sun damage, the US Congress passed the Sunscreen Innovation Act to accelerate the review process of these products. However, within seven months, all eight applications were rejected due to lack of data for safe use. The reason for such discrepancies can be mainly attributed to the fact that the EMA categorizes sunscreens as cosmetics, whereas the FDA reviews them as over-the-counter drugs, requiring evidence for both safety and efficacy [8]. Because of the wide gap in costs to develop cosmetics versus drugs, the divergent approach by the two regulatory agencies represents an insurmountable obstacle preventing market expansion. Similar issues affect other chemicals that lie in a gray zone between cosmetics and therapeutics, such as products for hair loss, dental, and skin care (Table 1).

# **International Harmonization Efforts**

Drug regulatory officials have long been trying to resolve the inconsistencies affecting the development process of pharmaceuticals across different countries. In 1979, the FDA formed the International Affairs Staff to cooperate with international regulatory agencies. A year later, the World Health Organization (WHO) and the FDA hosted the first International Conference of Drug Regulatory Authorities. In 1990, Europe, US and Japan met for the first International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use to ensure a timely introduction of new medical products, mutual acceptance of research data, and improved protection of public health. The ICH continues to issue guidelines for the standardization of clinical practices and technical requirements for human drugs, including the establishment and management of quality control laboratories and the prompt dissemination of new information on serious adverse drug effects [9].

Recently, both the FDA and EMA are promoting an exchange of scientific knowledge across the two agencies. In 2005, the FDA, EMA, and the European Commission finalized seven initiatives to share information involving accelerated approval, design issues, and post-marketing commitments. The two agencies hold monthly teleconferences to discuss pending regulatory decisions, reviews, requests for discontinuing clinical trials, and any significant changes in statistical analyses [10]. In addition, through the Transatlantic Economic Council, both the US and EU are seeking to deepen cooperation between regulatory authorities and reduce international duplication of inspections [11]. In 2011, the agencies launched a pilot program to jointly assess quality-by-design elements to review the

FDA	EMA
Similarities	
Common Objectives	
Adherence to ICH guidelines	
Seeking improved international guidelines	
Require preclinical and clinical (3 phases) testing	
Accelerated approval tracks	
Recommend market suspension	
Differences	
Central authority	Member state representation
Clinical trial supervision	No clinical trial supervision
Final marketing approval	Makes recommendation
Symptom-specific assessments	Global patient outcome reports

Table 1: Similarities and differences of the drug review process in the US and EU.

science and risks of pharmaceutical development and ensure product quality [12]. Also, they have recently set up collaborative meetings on pharmacovigilance, focusing on biosimilars, oncological therapeutics, orphan medicines, and pediatric drugs [13]. Both agencies have promised to continue these activities to streamline and synchronize transatlantic regulation.

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## Conclusion

Presently, regulatory differences between the US and the EU can hinder the expansion of pharmaceutical markets. Structural and functional differences between the FDA and EMA necessitate adequate planning to navigate requirements to manufacture and commercialize medical products internationally. However, collaborative engagements between government agencies, health care advocates and industry leaders have pushed for a more comprehensive process bringing pharmaceuticals to the public more quickly and safely. Future regulatory standardization between agencies is necessary to reduce redundancy and accelerate the review process workload for the benefit of all stakeholders.

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