

Comparing FDA and EMA Decisions for Market Authorization of Generic Drug Applications covering 2017–2020

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Summary

The Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have ongoing collaboration on scientific, technical, and regulatory matters. Recently, the FDA compared their regulatory decisions on generic drug applications with those of the EMA during the period of 2017-2020. For the purpose of this comparison study, FDA focused on gathering information for generic drugs that were reviewed through the EMA centralized market authorization process. The EMA decision for those applications were reviewed and compared to FDA decisions for the same drug product that was submitted to the FDA by the same applicant. There was a 95% concordance to application review outcome for applications that were submitted to both FDA and EMA. Of note, this study did not evaluate the similarity of the data submitted in those applications. This preliminary examination of data demonstrates a high rate of agreement between FDA and EMA suggesting that they are reasonably aligned in terms of decisions on marketing approvals of generic drugs. It is worth noting that the FDA received a higher number of applications for each drug class in comparison to EMA.

The number of generic drug applications included in this comparison study is limited and therefore is considered a preliminary assessment. Some additional questions to investigate in the future may be understanding further, for instance: Are companies submitting similar supporting materials to FDA and EMA? Are both agencies using the same or similar assessment criteria while reviewing the supporting materials? How similar are FDA and EMA inspections at the sites where bioequivalence studies are conducted?

The Question

To date, no comparisons of the decisions of FDA and the EMA regarding generic drug applications have been conducted. Understanding the similarities and differences in the regulatory landscape and the generic drug approval process between the U.S. and the EU could lead to a narrowing of the differences in the time to generic drug approval for generic drug applicants and could ultimately optimize patient access to generic drugs. Experience in the U.S. demonstrates that availability of more generic drugs generally leads to lower drug costs. As a preliminary screening for the research covered in this paper, FDA and EMA were judged to be reasonably aligned in terms of decisions made regarding many generic drug approvals [1-2].

Note: this current limited review of FDA and EMA 2017-2020 data along with a narrow literature review did not assess whether applicants submitted similar supporting materials to both Agencies during the designated time period.

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The History

Generic drugs remain a public health priority for the U.S. Food and Drug Administration, playing a pivotal role in increasing access to more affordable medications for the American public. Currently, 90% of prescriptions in the U.S. are dispensed as generics saving the health care system close to \$2.4 trillion dollars in the past decade alone [3]. Generic drug development and manufacturing has become an increasingly globalized endeavor urging a concerted effort for regulatory convergence and collaboration among the leading drug regulatory authorities [4]. An assessment and evaluation of regulators' expectations for generic drug development and standards for therapeutic equivalence is critical to facilitating more global alignment. Examination and comparison of decisions (i.e., approvals and non-approvals) on applications may provide a better understanding of how agencies deliberate.

The FDA and EMA have continued efforts towards convergence of regulatory standards for the development of generic drugs. The latest effort is the *Generic Drug Cluster* established in 2021 by FDA/Center for Drug Evaluation (CDER)/Office of Generic Drugs (OGD). This Cluster was launched with a vision to increase the alignment and transparency of standards for market approvals of generic drugs.

This Study

In the U.S., there is one process for generic drug approvals.¹ After a pharmaceutical company submits an Abbreviated New Drug Application (ANDA), FDA conducts a rigorous review of the materials and data submitted to ensure the generic drug product performs in the same manner and is substitutable for the reference listed drug [5]. In the EU, the process allows applicants numerous routes, allowing a pharmaceutical company four methods of getting a generic drug approved; national, mutual recognition, decentralized, and centralized authorization processes [6]. Per the 2019 EMA annual report, 90% of the medicines, mainly generic drugs, entering the EU market were approved through the national, mutual, or decentralized process.

In this study of generic drug applications, our objective was to compare FDA and EMA decisions over four calendar years, 2017–2020, as a window to the impact of the agencies' activities in technical collaboration. We examined applications for which the two agencies had differing outcomes in terms of approval, assessing the scientific and regulatory reasons underlying these differences.

The information for the EMA marketing authorizations during 2017-2020 and the list of approved and nonapproved generic drugs submitted to EMA was extracted from Annex 10 of the EMA published annual reports and the monthly Committee for Medicinal Products for Human Use (CHMP) reports [7]. The information for authorization of generic drugs and ANDA

¹ FDA also allows for 505(b)(2) applications, which are New Drug Applications that allow for greater flexibility than ANDAs as to the characteristics of the proposed product. For additional information, see the guidance for industry, *Determining Whether to Submit an ANDA or a 505(b)(2) Application* (May 2019).

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submissions in the U.S. was extracted from the FDA’s Document Archiving, Reporting and Regulatory Tracking System (DARRTS) database. The FDA database is not publicly available.

Generic drug applications received by EMA for a period of 4 years (2017-2020) were identified, and the number of approved drug applications by EMA and FDA (years of approval were not limited to 2017-2020) were compared. EMA, over the 2017-2020 time period, approved 61 drugs applications and, for the same period, FDA approved 3,243 generic drug applications (Table 1).

Table1. Generic drug marketing applications approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA)

YEAR	Generic Drug Applications Approved by EMA	Generic Drug Applications Approved by FDA
2017	22	843
2018	9	810
2019	15	836
2020	15	754
TOTAL	61	3,243

In comparing the unique generic drugs submitted for approval, the preliminary results found there were 42 unique reference products for 61 application approvals. For example, if a product was submitted by three different applicants, it was enumerated as a unique generic drug. Comparing these unique drug products, FDA approved 31. The 11 drugs remaining were either not approved by the FDA because they were still being assessed, received a complete response letter, or they were tentatively approved.

The study further identified unique generic drug applications submitted by the same applicant to FDA and EMA, comparing the regulatory decision outcome. The study demonstrated that 17 drugs were approved by both FDA and EMA. Four drugs were approved by EMA while FDA was still in the review process. Conversely, EMA did not approve erlotinib (applicant withdrew the application in 2020) and fingolimod generic drug applications, both of which were approved by the FDA. Only one drug was not approved by both regulatory agencies due to similar concerns with quality and manufacturing processes.

The preliminary review of data supports the similarities in the approval process between FDA and EMA for a company submitting the same drug. However, there are a few differences such as: difference in time when applications are submitted, different supporting materials, different

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reviewing criteria used by the regulatory agencies, and difference in legislative requirements and patent laws. Exploring these differences in depth could provide a deeper understanding on the approval process and feasibility of convergence of generic drug standards for the development of generic drugs.

Additionally, though outside the scope of this data review, we found that FDA and EMA seldom approved drugs in the same year. In 4 years, only five drugs were approved in the same year by both Agencies. In many situations, the difference in approval timeline exceeded several years. FDA approved tacrolimus, anagrelide, paclitaxel generic drug products 8, 12, and 17 years, respectively, before EMA. This difference in approval years seems predominately driven by a few factors such as: when FDA and EMA received the applications, the differences in the European Union (EU) and the U.S. patent laws and exclusivity statutes, and the agencies' reviewing processes.

The Results

In the cohort of agency decisions from 2017 to 2020 that were reviewed in this study, we found high concordance in the agencies' final decisions for applications that were submitted by the same applicant. Based on the data review of the 2017-2020 time period, our analysis found that the centralized generic drug approval process at EMA was similar to FDA however the findings of the study should be assessed within the scope of its limitations. It should also be noted that further review and analysis should be conducted to garner more comparative information for generic drug approvals between FDA and EMA.

The Opportunity

Employing mutually agreed upon generic drug development processes could reduce development barriers and minimize duplicate efforts that influence both the availability of safe, effective, and affordable treatments for patients and the sustainability of treatment costs. Efforts to standardize generic drug standards may, in some cases, result in lower drug development costs and a more simplified and consistent approach to generic drug development.

Additionally, further reviews of data, literature reviews, and audit-style studies to examine application approvals could quantify and illuminate each agency's regulatory conclusions and the reasoning for divergent conclusions among agencies. Continuous monitoring of generic drug approvals by both Agencies could allow for the assessment of the impact of FDA and EMA joint engagements which could help identify opportunities for further collaboration and more advice to the generic drug industry about both Agencies current thinking which could lead to more generic drug approvals - a potential cost-savings benefit for American consumers.

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