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The Food and Drug Administration reports provided more data but were more difficult to use than the European Medicines Agency reports

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Abstract

Objectives: To compare the accessibility, comprehensiveness, and usefulness of data available from the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) drug reports.

Study Design and Setting: This is a cross-sectional study. All new molecular drugs approved between January 1, 2011 and December 31, 2012 from the FDA and EMA Web sites were eligible.

Results: We included 27 drug reports. Most were searchable, but the FDA table of contents did not match the file's page numbers. Several FDA documents must be searched compared with a single EMA document, but the FDA reports contain more summary data on harms. Detailed information about harms was reported for 93% of the FDA reports (25 of 27 reports) and 26% of the EMA reports (7 of 27 reports). The reports contained information about trial methodology but did not include trial registry IDs or investigator names. All reports but one contained sufficient information to be used in a meta-analysis.

Conclusion: Detailed data on efficacy and harms are available at the two agencies. The FDA has more summary data on harms, but the documents are harder to navigate. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/3.0/).

Keywords: Unpublished data; Systematic reviews; Drug regulation; Harms; FDA; EMA

1. Introduction

Doctors and decision makers cannot depend solely on articles published in medical journals. Articles are often biased [1,2], and some studies are partially published or not published at all [3]. Drug regulators have access to additional data through the companies' approval applications, for instance individual patient data on harms and analysis of efficacy data for multiple outcomes. In the Food and Drug Administration (FDA) drug reviews, some of these data are reported and can provide useful unpublished data for systematic reviews [4−8]. Although unpublished data can be obtained from FDA and, more recently, the European Medicines Agency (EMA) websites, they are rarely used in meta-analysis [9,10]. Difficult access to the FDA Web site could be part of the explanation [11] and other explanations could be lack of guidance on when and how to access data from regulators. Both the FDA and the EMA have made recent changes to the types of information they make available to the public. The purpose of this study was to compare the accessibility, comprehensiveness, and usefulness of information available on the FDA and EMA Web sites.

2. Methods

We identified all new molecular entities approved by the FDA from January 1, 2011 to December 31, 2012 through their Web site (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm) and paired them with corresponding EMA drug approvals (http://www.ema.europa.eu). As in previous studies [7,12], biologics, orphan drugs, and diagnostics were excluded because they are reviewed using a

Conflict of interest: All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author). J.B.S. and L.B. declare that they have no conflicts of interest. M.A.S. worked as a paid intern at Genentech (June 2011 to August 2011) and served as a paid liaison for Genentech at University of California, San Francisco (November 2011 to July 2013).

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What is new?

- Most FDA and EMA reports described trials in sufficient detail to enable them to be included in a meta-analysis.
- Most FDA reports contained detailed information about harms whereas the EMA reports did not.
- The information on the FDA site is harder to navigate, in general, than the information on the EMA site.
- Both agencies should be searched by researches conducting reviews.

different approval process. New molecular entities from the EMA Web site (http://www.ema.europa.eu) were also identified in the same time period and paired with the corresponding FDA approval reports.

2.1. General description of drugs and documents

The medical review was our primary FDA resource, but we also extracted information from the approval letter, the Risk Evaluation and Mitigation Strategies (REMS), and the risk assessment reviews when available. For EMA-approved drugs, we examined only the European public assessment reports.

To determine how accessible the information was, two researchers (J.B.S. and M.A.S.) assessed whether each regulator provided structured reports, number of pages in the reports, a table of contents, a file that is searchable using text words, reviews in several languages, and lay summaries and whether it was possible to use direct Web links to resources.

To estimate how comprehensive the information was, we assessed whether information was redacted and, if so, whether a reason for the redaction was given and whether each regulator reported on unapproved drugs and relayed internal communications between reviewers and external communications between the applicant and the agency. We also assessed if the original trial protocols or the full trial reports were available and whether the agencies conducted additional statistical analyses.

2.2. Trial characteristics and efficacy data

We assessed the type of trial data that were available from each regulator and whether useful data for meta-analysis were available. Two researchers (M.A.S. and J.B.S.) independently assessed whether the FDA and EMA reports provided (1) an overview of the pivotal trials (the trials that were the basis of the clinical evaluation of the drug), (2) summary reports of each pivotal trial, (3) the number of pivotal trials and other submitted trials included, (4) the ClinicalTrials.gov ID for each trial, (5) names of the investigators, and (6) conflicts of interest among investigators. For the pivotal trials, the two researchers determined whether the inclusion and exclusion criteria for the trials were specified, whether outcomes were specified, whether numerical results were only available in a pooled format, and whether the efficacy results were presented in a manner that would allow for their inclusion in a meta-analysis (i.e., whether standard deviations and number of individuals were reported along with the numerical efficacy data).

2.3. Harms data

Two researchers (M.A.S. and J.B.S.) independently determined whether adverse event tables were present; whether safety data were provided for all completed trials or only for the indications being reviewed in the application; whether all important harms were reported (defined as common adverse events, mortality, serious adverse event, and withdrawals due to adverse events); whether numerical data on harms were reported; whether a risk management plan was included; whether regulators required further studies, follow-up on existing trials, or labeling restrictions; and whether REMS (FDA) or educational materials (EMA) were required by either or both agencies.

Any discrepancies between the two coders were discussed with the third author (L.B.). We planned a descriptive analysis of the differences between the data provided by the EMA and the FDA. We calculated the percentage of our binary outcomes.

3. Results

3.1. Drug characteristics

We found 57 new molecular entities approved by the FDA between 2011 and 2012; 14 orphan drugs and three diagnostic drugs were excluded. Another eight drugs were excluded for not having a corresponding approval on the EMA Web site (presumably the drug approval was never pursued in the European Union), four had only a pediatric plan (which we interpreted as pending), six had a pending status, and two had been withdrawn by the EMA, leaving 20 pairs approved by both agencies as of August 1, 2013. A similar search of the EMA Web site identified 50 new molecular entities approved in the same time period. We excluded 20 orphan drugs, one diagnostic drug, three with no FDA matches, two that were not approved by the FDA, and finally one in which the approval dates between the two agencies were more than 10 years apart and we believed that such a comparison would not be fair. The remaining 23 pairs identified through the EMA database were merged with the 20 pairs found in the FDA database to provide us with a final sample size of 27 unique pairs of drugs after duplicates were removed (Fig. 1). The most