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Research Briefs

Examination of risk evaluation and mitigation strategies and drug safety in the US

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Abstract

Background: The Food and Drug Administration Amendment Act of 2007 (FDAAA 2007) enabled the US Food and Drug Administration (FDA) to require risk evaluation and mitigation strategies (REMS) for a drug or biologic to ensure that its benefits outweigh the risks.
Objective: This study sought to evaluate REMS approved and released by the FDA since the program inception in 2008, to assess the characteristics of REMS approved and to calculate the time lag between FDA drug application approval and REMS approval.
Methods: Data were derived from Approved Drug Products with Therapeutic Equivalence Evaluations, Approved REMS and Drugs@FDA. Data included generic availability, application type and approval date, therapeutic class and FDA review class, orphan designation, priority review and market status.
Results: The FDA approved REMS for 259 marketing applications (217 new drug applications -NDAs, 10 abbreviated NDAs, and 32 biologic license applications) in the study period. The FDA granted orphan designation to 11.4% of active ingredients with REMS and priority review to 38.4% of the NDAs with REMS. The largest number of REMS approvals was for nervous system products (31.8% of total approved REMS) and antineoplastic and immunomodulating agents (15.3%).
Conclusions: The FDA approved REMS for one in three biologics and one in thirteen chemical entities available in the market. A pharmaceutical product can be in the market for an average of 14 years before the FDA identifies and evaluates the risk problems that warrant the approval of a REMS.

Keywords: FDA; Drug safety; Risk evaluation and mitigation strategies; Drug regulation

Background

The Federal Food, Drug, and Cosmetic Act (FDCA) entitles the FDA to authorize the marketing of pharmaceuticals that are safe and effective for use under the conditions included in the label (FDCA Section 505(d), 21 U.S.C. 355(d).[1] The risk of inappropriate utilization of pharmaceuticals has long been recognized by the FDA.[2] The Prescription Drug User Fee Act of 2002 required FDA to produce guidance for the

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pharmaceutical industry on risk management activities for chemical entities and biologics.[3] In 2005, the FDA published guidance for risk minimization action plans (RiskMAPs). A RiskMAP was a program aimed at minimizing a known risk of a pharmaceutical product while preserving its benefits.[4]

The Food and Drug Administration Amendment Act of 2007 (FDAAA) enabled the FDA to require a risk evaluation and mitigation strategies (REMS) for any pharmaceutical product to ensure that a drug's benefits outweigh its risks. REMS are strategies to manage a known or potential serious risk associated with drugs and biologics.[3,5,6] The FDA may approve a REMS at the time of drug approval or after the drug is marketed if new safety information becomes available. The FDA determines if a REMS is necessary based on several factors including the estimated size of the population likely to use the drug; the seriousness of the disease or condition that is to be treated; the expected benefit of the drug; the expected or actual duration of treatment; the seriousness of any known, potential, or previous adverse events; and whether the drug is a new molecular entity (i.e., the drug has not been approved before for marketing in the US).[6] Pharmaceutical products that had a RiskMAP or elements to assure safe use also may be deemed to have in effect FDA approved REMS.[7]

A REMS may consist of a medication guide intended to provide information for the safe and effective use of a drug,[5,8–10] a patient package insert, a communication plan to health care providers (e.g., web-based educational materials, presentations to health care professionals by medical science liaisons), elements to ensure safe use (ETASU) or a combination of these items.[6] An ETASU requires documentation and assurance of training, experience, or specialty credentials for the drug prescriber and certification requirements for the drug dispenser. An ETASU could also require dispensing of the drug only in certain health care settings, documentation of safe-use conditions, patient monitoring, and patient enrollment in a registry.[3,6,11]

In November 2011, the FDA changed its policy related to REMS containing only medication guides.[12] The new FDA policy establishes that a medication guide will be part of a REMS when it includes elements to assure safe use or if the FDA determines that having the medication guide without a REMS will not be sufficient to ensure that the benefits of the drug outweigh the risks.[12] Pharmaceutical companies may also request release of an approved REMS when the only REMS elements are a medication guide and a timetable for assessment.

In spite of the large number of REMS approved by the FDA and their important effect on patient safety, there are no studies assessing the characteristics of the REMS. Assessing whether the FDA's ability to require REMS after FDAAA 2007 has yielded any changes to ensure benefits outweigh risks for drugs and biologics is a timely question as managing drug safety risks for patients continues to be an increasingly difficult challenge. Thus, this study sought to analyze secular trends in REMS approved and released by the FDA in the period January 2008–May 2012, to assess the characteristics of REMS approved by the FDA, and to calculate the time lag between FDA drug application approval and REMS approval.

Methods

Data were collected from the FDA Approved Drug Products with Therapeutic Equivalence Evaluations. Relevant characteristics of pharmaceutical products were extracted from the list of Approved Risk Evaluation and Mitigation Strategies (REMS) and the Drugs@FDA databases. Data collected from the FDA website included the application type (i.e., NDA, Biologic Licensing Application (BLA) or Abbreviated NDA (ANDA)), marketing application number, and marketing application approval date.

The investigators identified whether the pharmaceutical product was granted priority review or orphan drug designation for the first approval of the product, and whether they were discontinued from the market. A priority review drug is defined by the FDA as a product that is a significant improvement compared to marketed products or provides safe and effective therapy where no satisfactory alternative therapy exists. All non-priority review drugs were considered standard review drugs. We also identified whether the drug was approved by the FDA as an orphan drug (i.e., the drug has utility in a disease affecting fewer than 200,000 people in the US or there is no reasonable expectation that costs of research and development of the drug for the indication can be recovered by sales of the drug in the US). Market status information was also collected from FDA databases. We considered a drug to be discontinued from the US market as of May 31, 2012 if it was no longer