Risk evaluation and mitigation strategies: what is the impact of the prescription drug user fee act of 2012?

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Background

The Food and Drug Administration (FDA) once relied solely on clinical trials for safety information prior to product market entry. This information provides valuable estimates of population risk; however, some products require additional precautionary measures to ensure that its benefits outweigh its risks in the general population.[1] For instance, Accutane (isotretinoin) was approved in 1982 for the treatment of severe recalcitrant nodular acne. Although this drug is known for its teratogenic properties, over 2,000 pregnancies have been exposed to the medication resulting in spontaneous abortions or fetal abnormalities.[2] To further manage product risks, the FDA incorporated drug surveillance programs and implemented regulations to strategically minimize adverse events associated with isotretinoin. The overall goal of these strategies was to inform patients of possible medication risks, prevent unneeded exposure, and minimize drug-drug or disease-drug interactions.[3]

Risk Evaluation and Mitigation Strategies (REMS) was developed for drugs and biologics which pose additional safety risks to patients. In 2007, the Food and Drug Administration Amendments Act (FDAAA) authorized the FDA to require a REMS for products where further safety measures beyond labeling may be necessary.[4] REMS was designed similarly to Risk Minimization Action Plans (RiskMAPs) which were introduced in 2005. However, RiskMAPs had issues surrounding government enforcement.[5]

Each REMS is customized and set by the sponsor company with review and approval by the FDA. They can be initiated for a single product or for an entire drug class.[6] Medications and biologics may require extensive risk management efforts such as "Elements to Assure Safe Use" (ETASU) which may involve additional prescriber training, certification of distributors or pharmacies, and patient registries. The components can also be less comprehensive, such as a communication plan to pertinent healthcare providers or a medication guide. [1]

Since the initiation of REMS in 2007, there have been several medications and biologics that have needed a REMS, but were subsequently released from the requirements after further evaluation. The Prescription Drug User Fee Act of 2012 (PDUFA V) created an initiative aimed at generating a fully integrated system to implement and evaluate REMS in a uniformed fashion. As of September 2013, there are 64 active, individual REMS products along with 6 shared system REMS. Since implementation, 136 REMS have been released. [7] The value of REMS is arguably challenged given that 68% of all products requiring a REMS component were ultimately deemed unnecessary.

Objective

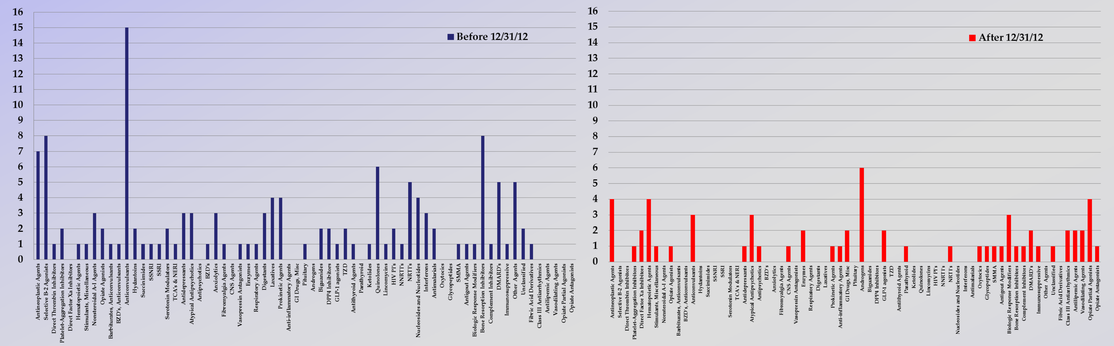
We chose to survey released and current REMS in order to reveal a defining factor for requiring a REMS component post-approval by the FDA.

Methods

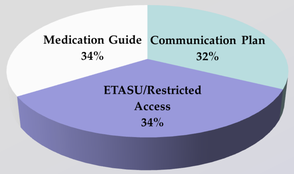
Prescription medications were evaluated based on whether they currently had a REMS component as part of their post-marketing commitment or if the drug had been released from REMS prior to December 31, 2012. The two groups were organized using Microsoft Excel and then stratified according to several factors including American Hospital Formulary System (AHFS) drug class, mechanism of action, indication and the type of REMS component attached to each drug approval. Descriptive statistics were used to compare drugs currently executing a REMS component to drugs that have been released from REMS prior to December 31, 2012.

Results

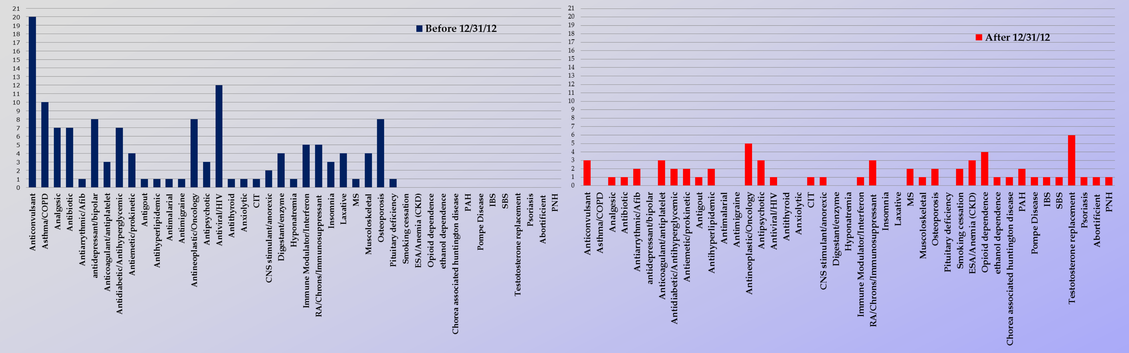
REMS by AHFS Class



Current REMS Components



REMS by Therapeutic Use



Discussion

AHFS classes with the most drugs (≥5 drugs) released from REMS prior to December 31, 2012 were antineoplastics, selective β2 agonists, anticonvulsants, quinolones, NRTIs, bone resorption inhibitors, and DMARDS. AHFS classes with the most drugs (≥3 drugs) that remained on REMS after December 31, 2012 were antineoplastics, hematopoietic agents, anticonvulsants, atypical antipsychotics, androgens, biologic response modifiers, and partial opiate agonists. The implementation of PDUFA V had the most significant impact on anticonvulsants with a total of 11 drugs released from REMS. Antineoplastics and anticonvulsants were both the most commonly released and remaining REMS by AHFS class. According to these results, the value of REMS may be limited by the amount of time it exists; however there is a lack of data showing if a REMS is even useful at all.

Therapeutic areas with the most drugs (≥10) released from REMS prior to December 31, 2012 were anticonvulsants, asthma/COPD, and antiviral/HIV. Therapeutic areas with the most drugs (≥4 drugs) that remained on REMS after December 31, 2012 were antineoplastic/oncology, opioid dependence, and testosterone. Current REMS are almost evenly divided between required medications guides (34%), restricted access/ETASU (34%), and communication plans (32%). The vast reduction in the number of med-guide only REMS after PDUFA V has shown a shift in the content and implementation of REMS.

The results show that there needs to be measurable outcomes in order to assess the effectiveness of a REMS especially for novel classes and orphan diseases where there is still a great deficit of knowledge. In the future, we expect to see an increasing number of drug approvals in the oncology and rare disease space which could change the face of drug safety. Risk management is an evolving field that needs to develop a concrete methodology in order to assess how effectively REMS prevent adverse outcomes.

Limitations

There were various limiting factors to this investigation, primarily due to the lack of information publicly available. Information regarding the types of REMS and specific dates associated with the implementation and release of REMS was not always accessible. Furthermore, since there is not a systematic approach to the release strategy of REMS, it was difficult to pre-determine endpoints to study. Our investigation was also limited to descriptive statistics and a cross-sectional analysis of released and current REMS. In order to draw conclusions regarding the effectiveness of REMS over time, more research is needed to analyze the prevalence of adverse outcomes in these patient populations.

Conclusions

The aim of this investigation was to examine the differences between medications requiring a REMS pre and post PDUFA V. The data presented shows changes in drug development and indications pursued by manufacturers over time; suggesting that specific therapeutic areas necessitate less risk management than once thought. Overall more transparency is needed for the implementation and evaluation of REMS programs. Continued research should be pursued in order to analyze these relationships further.

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Disclosure

All authors are affiliated with the Rutgers Pharmaceutical Industry Fellowship program and are employees of Rutgers University.