

Risk Evaluation and Mitigation Strategies (REMS) and How They Impact Biostatistics and Statistical Programming Groups

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ABSTRACT

The Food and Drug Administration Amendments Act (FDAAA) of 2007 expanded the regulatory authority of the FDA with regard to risk management programs, creating a new program called Risk Evaluation and Mitigation Strategies (REMS). The REMS requirements build on the Risk Minimization Action Plans (RiskMAP) which were instituted in 2005. As a result, the requirements placed on drug makers for post-marketing safety and risk assessment have been growing. Approximately one-third of new drug approvals have REMS associated with them, 16 of the 30 existing RiskMAP programs have been transitioned to REMS programs, and the FDA may be moving towards using REMS for mitigation of off-label product use. This leads to more work for departments supporting REMS activities including Biostatistics and Statistical Programming. Often the types of data that must be collected and analyzed for REMS are non-standard, less controlled, and may come from an assortment of sources with which these groups do not typically work. While REMS present new challenges to drug makers, they also bring opportunities including enhanced labeling, better communication with patients and providers, and strengthened ties to healthcare professionals. These opportunities can be attractive to many functional areas in the company, including Regulatory Affairs, Medical Affairs, Marketing, Drug Safety, and Clinical Development. In this paper I will present some background and history of the FDA's risk management efforts and some discussion of how the current requirements may be implemented, as well as some of the challenges and opportunities that they present.

BACKGROUND AND HISTORY OF REMS

In order to reap the benefits that new drugs offer, it is necessary to manage the risk that comes with them. The FDA defines risk management as 'the overall and continuing process of minimizing risks throughout a product's lifecycle to optimize its benefit-risk balance'. (Guidance for Industry Development and Use of Risk Minimization Action Plans (March, 2005)) To do this successfully, the risk must be accurately assessed and then interventions must be developed to minimize it. Early attempts to address this issue by the FDA began with the Pure Food and Drug Act of 1906 which prohibited interstate commerce in adulterated or misbranded drugs. It also required labeling to indicate the presence and amount of selected dangerous or addicting substances in drugs such as alcohol, morphine, heroin, and cocaine. The Pure Food and Drug Act did not grant enough authority for enforcement which led to some tragic outcomes, notable among them was Elixir Sulfanilamide which in 1937 resulted in 107 deaths. This product contained an untested chemical called diethylene glycol which is chemically related to antifreeze and proved to be poisonous to humans. Created in the wake of this tragedy was the Food Drug and Cosmetic Act of 1938 which required all new drugs to be proven safe. This law also strengthened enforcement powers and added more detailed labeling requirements. The Thalidomide tragedy of the late 1950s and early 1960s resulted in further strengthening of the laws regulating drugs, paving the way for the current era of risk management. The Kefauver-Harris Amendments of 1962 required new drugs to be proven both safe and effective. In addition, drug advertising, labeling, and planned clinical trials all had to be approved by the FDA.

The Controlled Substances Act of 1970 began to formalize risk management by adding black box warnings and 'Dear Healthcare Provider' letters. This was followed soon after with the implementation of patient package inserts. During the 1980s, language describing teratogenicity risks began to be added to contraindications, warnings and precautions sections of the package insert, and pregnancy prevention programs were mandated for some drugs. Thalidomide was eventually approved for treatment of leprosy in 1998 with a risk management program called The System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.™). Medication guides were introduced in the late 1990s for some drugs with serious health risks. These developments were eventually consolidated into several new guidance documents issued by the FDA including; *Premarketing Risk Assessment*, *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment*, and *Development and Use of Risk Minimization Action Plans (RiskMAP)*.

Even though much progress had been made, the Institute of Medicine of the National Academies released a report in 2006 titled *The Future of Drug Safety: Promoting and Protecting the Health of the Public* which discussed continuing deficiencies with post-marketing drug safety. This report combined with some highly publicized drug withdrawals resulted in further regulation stipulated by the Food and Drug Administration Amendments Act (FDAAA) of 2007 which expanded the regulatory authority of the FDA with regard to risk management. The act granted the FDA authority to do the following:

- Require post-approval studies or clinical trials to assess a known or serious risk, or to learn more about a hypothetical serious risk.
- Require that new safety information be added to the product labeling.
- Require that companies submit Risk Evaluation and Mitigation Strategies (REMS) when deemed necessary to ensure that the product's benefits outweigh the risks

The REMS requirements built on the earlier RiskMAP program and were laid out in a draft guidance released in 2009. Elements which can be required as part of a REMS plan include; medication guides or patient package inserts, communication plans, elements to assure safe use (previously known as distribution restrictions), implementation plans, and a timetable for submission of assessments. A medication guide is a document written for patients highlighting important safety information about the drug. A communication plan is designed to educate healthcare professionals on the safe and appropriate use of the drug. All elements of REMS plans must be assessed at 18 months, 3 years, and 7 years after implementation.

As a result of these developments, the requirements placed on drug makers for post-marketing safety and risk assessment have been growing. Approximately one-third of new drug approvals have REMS associated with them, 16 of the 30 existing RiskMAP programs have been transitioned to REMS programs, and the FDA may be moving towards using REMS for mitigation of off-label product use. Some companies have decided to use REMS components including patient registries, education programs, and specialized distribution systems even when they are not required to. All of this means more work for departments supporting REMS activities including Biostatistics and Statistical Programming groups.

HOW REMS AFFECTS BIOSTATISTICS AND STATISTICAL PROGRAMMING GROUPS

Most of the activities related to REMS are carried out by groups outside of Biostatistics and Statistical Programming, including Drug Safety, Regulatory Affairs, and Medical Affairs and there are outside organizations specializing in implementing certain components like training and education programs. Where Biostatistics and Statistical Programming groups are most likely to become involved is with the assessment of REMS initiatives. Often the types of data that must be collected and analyzed to do these assessments are non-standard, less controlled, and may come from an assortment of sources which these groups do not typically work with.

Assessments for medication guides and communication plans may take the form of surveys to determine whether patients are receiving the guides, understand them, and can demonstrate knowledge or to determine providers' awareness of risks and knowledge of how to minimize them. Biostatisticians may be asked to develop sampling plans to assure that the data is representative of the population and Statistical Programmers may be asked to summarize the responses for inclusion in regular assessment reports. The larger impact is likely to come from Elements to Assure Safe Use (ETASU) which can involve special training and certifications for providers and pharmacists, controlled settings for dispensing drugs, patient monitoring, and patient registries. The patient registries created for this purpose can be a treasure trove of data which will be of interest to all areas of the organization and can be combined with additional data collected in sub-studies to further clarify or stratify the risk profile of a drug. Data collected from these sources may be included in sBLA or sNDA submissions to enhance risk stratification language in the label or as evidence to support removal of warnings.

Aside from data collection instruments and programs developed in-house by drug makers, there are many existing data sources which could be used to assess the effectiveness of REMS programs. Examples are large automated claims databases, national surveys, market research data, feedback from existing drug information lines, metrics from website traffic, order tracking for educational material, pharmacovigilance reports, product complaints, and some commercially available tools. The FDA is working towards standardizing some of the assessment tools which will lead to efficiencies in analyzing the data. This will be especially true for drug-class REMS which are implemented for whole classes of medications with particular safety concerns as was done for long acting opioids in early 2009. In the recently published *PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017* the FDA has pledged by the end of fiscal year 2013 to issue guidance on how to determine if a REMS is needed and by the end of fiscal year 2014 to issue guidance on methodologies for assessing REMS.

OPPORTUNITIES

With increased use of REMS plans, the FDA hopes to increase the likelihood that unforeseen safety trends will be detected early, get a clearer understanding of the safety profile of certain drugs, and gain confirmation of the initial risk-benefit assessment at the time of approval. Healthcare providers can benefit from components of REMS that track outcomes for their patients and collect information on overall and patient subgroup trends. While REMS present new challenges to drug makers, they also bring opportunities for collection of information on competing products, enhanced labeling, better communication with patients, strengthened ties to healthcare providers, and a platform to conduct sub studies. These opportunities can be attractive to many functional areas in the company including

Regulatory Affairs, Medical Affairs, Marketing, Drug Safety, and Clinical Development. Biostatistics and Statistical Programming groups need to be involved with the planning and design of patient registries and assessment programs to ensure that the data is collected in a way that lends itself to being analyzed and combined with other data. This will facilitate analyses which are subsequently requested and help maximize the value of the company's REMS efforts.

CONCLUSION

The increased post-marketing requirements ushered in with the recent FDAAA legislation, including REMS programs, will create some burdens for drug makers and healthcare providers. The FDA and industry are working to streamline and standardize these requirements and over time the burden will be eased as REMS activities become more integrated into operating procedures. All stakeholders stand to gain by having more robust risk-benefit analysis capabilities, chief among them are the patients. Patients will not only gain by being better protected from potentially adverse side effects of drugs, but the protections that REMS provide to drug makers, providers, and the FDA may lead to the approval of beneficial drugs which may not have been otherwise approved.

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