

S. 3807, the Enhancing Drug Safety and Innovation Act of 2006

S. 3807, the Enhancing Drug Safety and Innovation Act of 2006, was introduced by Senator Mike Enzi and Senator Ted Kennedy on August 3. The bill contains four titles: drug safety; establishment of the Reagan-Udall Institute for Applied Biomedical Research; clinical trials registry and results databases; and reform of conflicts of interests on FDA advisory committees. S. 3807 reflects the comments and input of dozens of stakeholders, including the Food and Drug Administration, patient and consumer groups, industry associations, individual companies, and scientific experts. Its provisions are outlined below.

Drug Safety

It is not possible to know everything about a drug at the time of approval. Requiring sponsors to obtain all safety information before allowing the drug on the market would unduly delay patient access to new therapies. The bill creates a framework for better pre-approval planning of how sponsors and FDA will identify, assess and manage risks post-approval. The result will be both a more efficient and effective way to obtain safety information, without compromising access.

FDA has post-approval authorities now, but they are not always the ideal tools to do what is needed. For example, if the agency believes a labeling change is necessary, it can request that the product sponsor make the change. If the product sponsor does not agree to the change, the agency cannot order the labeling change. FDA may initiate a misbranding action in the courts, but a sponsor who disagrees about a labeling change will contest the litigation, which can take months or even years to resolve. Moreover, such enforcement actions - seizing the product, or enjoining its distribution once FDA proves misbranding in court - may have the negative consequence of removing the drug from patients' hands.

In most cases, the agency and the sponsor will reach agreement about how to address a safety concern. However, there is currently no clear way to reach a decision and move forward to action when there is disagreement. By creating a structured framework for resolving safety concerns, the bill solves this problem.

The framework:

Risk Evaluation and Mitigation Strategy (REMS)

Under the Enhancing Drug Safety and Innovation Act, FDA would begin to approve drugs and biologics, and new indications for these products with risk evaluation and mitigation strategies (REMS). The REMS is designed to be an integrated, flexible mechanism to acquire and adapt to new safety information about a drug. Sponsors would propose a REMS and FDA would approve it after structured discussions. The sponsor and FDA will assess and review the REMS at least annually for the first three

years, as well as in applications for a new indication, when the sponsor suggests changes, or when FDA requests a review based on new safety information.

Minimal Elements of a REMS:

Every REMS would have the following elements:

- The drug's FDA-approved professional labeling;
- 15-day, quarterly, and annual reports of adverse events for the drug;
- A pharmacovigilance statement that explains and justifies whether standard adverse event reporting for the drug is adequate to assess known serious risks and to identify unexpected serious risks, or whether and what additional studies or clinical trials are needed;
- A timetable for periodic assessment of the REMS.

Additional Elements:

Based on the nature and magnitude of the safety issues with a particular drug, the drug's REMS may include one or more of the following elements, if specific criteria are met:

- Required distribution of a Medication Guide or patient package insert when the drug is dispensed;
- A communication plan to health care providers regarding elements of the REMS;
- Post-approval registries or epidemiological studies to assess signals of serious risks or to screen for serious risks in expanded patient populations, or, when necessary, clinical trials to assess signals of serious risks;
- Pre-clearance of advertising, specific disclosures in advertising, or a prohibition on DTC advertisements for no more than 2 years after approval when disclosures alone aren't adequate to protect public health;
- Restrictions on distribution and use for a drug that presents a serious risk to the public health but offers significant benefit to patients.

Currently, only about 30 drugs are approved with restrictions on distribution and use (what is known as a RiskMAP), and such restrictions are intended to remain an infrequent requirement under S. .

Timeframes:

Assessment, FDA review, and discussion of a drug's REMS would take place within set timeframes:

- In the context of an application or supplement, FDA must begin to discuss the proposed REMS with the sponsor at least 60 days before the drug user fee action deadline to ensure time for thorough review of the REMS and to minimize the chance that dispute resolution, if invoked, would delay regulatory action;

- If there is new safety information about a serious risk, FDA may order the sponsor to submit an assessment of a REMS and must begin discussions within a set time period;
- A sponsor may submit an assessment of, and propose modifications (which may include reductions) to, a drug's REMS at any time.

Dispute Resolution:

When there is disagreement between FDA and the sponsor about a drug's REMS, the drug's sponsor may initiate a structured dispute resolution process. This process will bring fairness, timeliness, and finality to the response to new safety information.

- The process begins by the sponsor proposing a REMS or assessing whether changes to an existing REMS are needed, and can be terminated by FDA and the sponsor reaching agreement at any point before the issuance of an order;
- After discussions begin between FDA and the sponsor regarding the proposed REMS, the sponsor may request review by the Drug Safety Oversight Board from day 15 until day 35;
- Both the sponsor's proposed REMS and FDA's alternative go to the next monthly meeting of the Drug Safety Oversight Board for review, or a specially-scheduled meeting can be called if the dispute needs quicker resolution;
- The Drug Safety Oversight Board reviews both proposals and makes recommendations to the Secretary within 5 days;
- The FDA issues a final order within 7 days of receiving the recommendations.
- From the time FDA/sponsor discussions begin, the dispute resolution process takes from 36 days to 89 days, depending on circumstances.

Compliance and enforcement:

A REMS requirement that is not working can, and should, be modified through the assessment process. Should a sponsor still fail to comply with a REMS requirement, however, FDA can enforce the requirement as follows:

- Non-compliance with an element of a REMS would be a prohibited act;
- Civil money penalties could be imposed for knowing violation of any REMS component.

Application to generic drugs:

A generic drug would be required to meet each element of a REMS except post-approval clinical trial requirements that were imposed on the drug before it lost patent protection.

Resources:

Drug user fees will be increased to review REMS proposals and assessments and for FDA's general drug safety surveillance.

Reagan-Udall Institute for Applied Biomedical Research

Title II of the Enhancing Drug Safety and Innovation Act would spur innovation by establishing a new public-private partnership at the FDA to advance the Critical Path Initiative and improve the sciences of developing, manufacturing, and evaluating the safety and effectiveness of drugs, devices, biologics and diagnostics.

The development of tools to evaluate medical products has not kept pace with discoveries in basic science. New tools are needed to better predict safety and efficacy, which in turn would increase the speed and efficiency of product development and evaluation. Creation of a new generation of performance standards and predictive tools will provide faster and more certain answers about the safety and effectiveness of products in development. This has enormous potential both to speed product development and increase safety.

This public-private partnership, known as the Reagan-Udall Institute for Applied Biomedical Research, will facilitate these improvements in drug, biologic, device, and diagnostic sciences by coordinating research activities between government regulators and academic and industry researchers.

Activities of the Institute:

- The Institute would identify and pursue research priorities to aid in the modernization of medical product development and enhancement of product safety so that research findings are quickly incorporated into regulatory regimes.
- The Institute would coordinate and participate in government research and development programs and award grants and establish collaborations to carry out research priorities.
- The Institute would broadly distribute the knowledge and intellectual property developed through this research to ensure that the fruits of the research are incorporated into the medical product development and evaluation processes.
- The Institute would sponsor scientific conferences or symposia to assist in the evaluation of new tools to assess the safety of therapeutic products.

Governance Structure of the Institute:

The Institute would be supported by Federal funds, which could be complemented by contributions from the pharmaceutical and device industries as well as from philanthropic organizations.

- The Institute would have a Board of Directors comprised of:
 - Government officials;
 - Pharmaceutical and device industry researchers;
 - Academic researchers; and
 - Patient and provider representatives.

- The Board of Directors would:
 - establish by-laws to carry out Institute activities;
 - award contracts and peer-reviewed grants;
 - select an Executive Director to oversee the day-to-day operations of the Institute; and
 - report to Congress annually on the support and operations of the Institute.

Clinical Trials Registry and Clinical Trials Results Database

Clinical trials are an essential part of drug development. However, issues such as patient recruitment and timely access to information add complexity and cost to trials. The current NIH database, ClinicalTrials.gov, is a listing of trials for serious and life-threatening conditions, so that patients can learn more about these trials and find out how to participate. However, not all clinical trials are required to register, and information about trial results important to providers and patients, particularly negative results, may or may not be released by sponsors. A central clearinghouse for information about clinical trials and their results would help patients, providers and researchers learn new information and make more informed health care decisions.

Clinical Trials Registry:

Title III of the Enhancing Drug Safety and Innovation Act would establish a publicly available database at NIH to enhance patient enrollment in clinical trials of drugs for any disease or condition and provide a mechanism to track subsequent progress of trials. This database would build on ClinicalTrials.gov, which would remain publicly accessible.

- Late Phase II, Phase III, and Phase IV clinical trials would be required to register.

- Information about the trial would be searchable by key data elements, and the entry would include the data set developed by the World Health Organization and accepted as the international standard. Information must be truthful, not misleading, and non-promotional.

- The information would be submitted within 14 days of the date the first patient enrolls in the trial.

Clinical Trials Results Database:

Title III would also establish a database to ensure that results of trials are made public, and that patients and providers have the most up-to-date information.

- Results of all Phase III and Phase IV clinical trials would be required to be submitted to the database. There would be a process instituted to determine whether and how to require submission of the results of late Phase II trials, since these results may contain commercially sensitive information.
- Basic pieces of information would be placed in searchable fields in the database, while the bulk of the results information would be in two summary documents (lay and technical). Both summary documents would be publicly available. There is not yet an agreed-upon set of international standards in this area, so S. specifies the data elements that must be submitted.
- Results would be submitted to the database one year after the trial concludes. If regulatory action or publication is pending, the results would not be publicly available until that is resolved, which would protect both commercially valuable trial results and the ability of researchers to publish their results.
- The submitted results must be truthful, not misleading, and non-promotional.

Compliance:

- There are a variety of tools to enforce compliance with the registry and results database requirements:
 - Submission to the registry database would be a requirement for an investigational new drug exemption;
 - Unless information for a trial of a drug is submitted to the both the registry and results databases, FDA would not be permitted to file an application for approval of the drug, and the application could not be reviewed;
 - If a clinical trial is funded from NIH or another Federal agency, but the trial is not registered or the results are not submitted, the grant money would not be released;
 - FDA and the Inspector General Office at the Department of Health and Human Services would review the content of submissions to the results database;
 - Medical journals would be able to query the database to determine whether or not results had been submitted, since many journals require submission of results to a database for publication; and
 - Failure to submit required information, or the submission of false, misleading or promotional information would be a prohibited act under the Federal Food, Drug, and Cosmetic Act.

Effect on other laws:

- State clinical trial databases would be preempted, and the fact of compliance with data submission requirements could not be used as evidence of off-label promotion of the drug.

Conflicts of Interest and FDA Advisory Committees

Title IV of the Enhancing Drug Safety and Innovation Act would make improvements to FDA's process for screening advisory committee members for financial conflicts of interest. FDA relies upon its 30 advisory committees to provide independent expert advice, lend credibility to the product review process, and inform consumers of trends in product development. Advisory Committee recommendations are non-binding on the agency, but the recommendations are usually followed.

Recently, questions have been raised about conflicts of interest that panel members on FDA Advisory Committees may have because of industry funding or other financial interests. When a potential conflict is identified, FDA considers whether the person's expertise is essential and whether the need for that person's service outweighs the risks of the potential for a conflict. Based on that evaluation, FDA has the statutory authority to grant a waiver and allow that person to serve.

Current FDA guidance on how to implement that authority contains inconsistent requirements that make it difficult to predict whether an individual under consideration will emerge as eligible for service, eligible only with a waiver, or recused. While the potential for a conflict should not automatically disqualify someone, a lack of transparency and predictability in how potential conflicts will be reviewed endangers the integrity of the review process. Finally, FDA faces a key challenge in identifying a sufficient number of people with the necessary expertise and a minimum of potential conflicts of interest to serve on advisory committees.

Evaluation of candidates for appointment:

- New candidates for appointment to advisory panels would be screened by FDA with the goals of identifying qualified candidates and minimizing potential conflicts of interest.
- FDA would be directed to enhance public nomination of individuals for service on advisory committees in order to expand the pool of qualified candidates.

Evaluation of panel members for service at a meeting:

- The categories of financial involvements used to evaluate a panel member for service at a panel meeting would be streamlined and clarified.

- FDA would be directed to define how interests imputed to an individual (such as financial interests of an employer) bear on eligibility for service on an advisory committee.
- FDA would be directed to standardize how individuals are evaluated for service on advisory committees across the centers of the agency.

Disclosure of information:

- The identity of panel members recused from service or who receive a waiver for service at an advisory committee meeting would be disclosed prior to a meeting.
- All financial involvements of panel members at a meeting would be required to be read into the public record of advisory committee meetings.

Review of past panel members:

- The HHS Inspector General would be directed to periodically evaluate current financial involvements of past advisory committee members to assess whether individuals are being rewarded for their past votes as members of an advisory committee.