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Drug Safety: A Side-by-Side Comparison of Bills in the 110th Congress

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Summary

Members of Congress and the public are increasingly concerned about the ability of the Food and Drug Administration (FDA) to ensure that the drugs sold in the United States are safe and effective. In November 2004, FDA asked the Institute of Medicine (IOM) to assess the current system for evaluating and ensuring drug safety and to make recommendations to improve risk assessment, surveillance, and the safe use of drugs. IOM released *The Future of Drug Safety: Promoting and Protecting the Health of the Public* in September 2006, and FDA issued its response in January 2007. The following drug safety bills have been introduced in the 110th Congress: S. 468 / H.R. 788, S. 484, and H.R. 1165.

Although the legislation and the IOM report address many of the same drug safety issues, the bills differ in their treatment of FDA authority to require action and to enforce compliance, comparative effectiveness studies, and how to fund any additional agency activities. For example, S. 468 / H.R. 788 would strengthen FDA's post-approval drug safety activities by creating a new Center for Postmarket Evaluation and Research for Drugs and Biologics. The other bills would leave these activities where they currently reside in the Center for Drug Evaluation and Research. All the bills would allow the FDA to penalize (through civil fines, injunctions, or withdrawal of marketing approval or licensure) drug manufacturers who did not conduct required postmarket studies or who failed to report study results.

The IOM committee recommended that Congress provide substantially increased resources to FDA to bolster its drug safety activities. S. 468 / H.R. 788 would authorize appropriations to carry out the bill's provisions, S. 484 would rely on user fees, expanding FDA's existing authority to use such fees, and H.R. 1165 does not address funding.

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Background

Members of Congress and the public are increasingly concerned about the ability of the Food and Drug Administration (FDA) to ensure that the drugs sold in the United States are safe and effective. Legislators, industry, the public, and FDA scientists have raised questions about FDA's collection and release of safety data, and whether the agency has the authority and resources to ensure adequate research over the marketing life of the pharmaceutical products it regulates.

In 2004, the regulatory, medical, and industry debate became very public with reports of cardiovascular hazards posed by the pain medicine Vioxx (one of several COX-2 nonsteroidal antiflammatory drugs then on the market), and of children facing increased risk of suicidal thoughts and actions when taking certain antidepressants (such as the selective serotonin reuptake inhibitors Paxil and Zoloft). Not only was Congress asking whether the manufacturers knew of these risks while continuing to market the drug, but also whether FDA should have known of the risks and done more to protect the public.

At the height of public and Congressional attention, FDA asked the Institute of Medicine (IOM) to "conduct an independent assessment of the current system for evaluating and ensuring drug safety postmarketing and make recommendations to improve risk assessment, surveillance, and the safe use of drugs." IOM released its report in September 2006.[1] FDA issued its response in January 2007 and noted relevant activities the agency has begun and others it has planned.[2] Among the planned activities are those in its proposal for a reauthorization of the prescription drug user fee program (PDUFA IV).[3]

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[1] Institute of Medicine (IOM), *The Future of Drug Safety: Promoting and Protecting the Health of the Public*, Alina Baciu, Kathleen Stratton, Sheila P. Burke, Editors, Committee on the Assessment of the US Drug Safety System, Board on Population Health and Public Health Practice (Washington, DC: National Academies Press, 2006).

[2] Food and Drug Administration (FDA), "The Future of Drug Safety — Promoting and Protecting the Health of the Public: FDA's Response to the Institute of Medicine's 2006 Report," January 2007.

[3] Congress first gave FDA authority to collect these fees with the Prescription Drug User Fee Act of 1992; reauthorized twice, the current authority expires Oct. 1, 2007. See CRS Report RL33914, *The Prescription Drug User Fee Act (PDUFA): Background and Issues for PDUFA IV Reauthorization*, by Susan Thaul.

In the meantime, several Members of Congress have introduced bills to address drug safety and FDA's role in protecting the public's health.

Report Highlights

This report provides a side-by-side comparison of:

- **Institute of Medicine:** recommendations in its September 2006 report, *The Future of Drug Safety: Promoting and Protecting the Health of the Public*;
- **Food and Drug Administration:** announced actions and plans to address problems identified in the IOM report;
- **S. 468 / H.R. 788** (the Food and Drug Administration Safety Act of 2007), introduced on January 31, 2007, by Senators Grassley, Dodd, Mikulski, and Bingaman, and Representatives Tierney and Ramstad;
- **S. 484** (the Enhancing Drug Safety and Innovation Act of 2007), introduced on February 1, 2007, by Senators Enzi and Kennedy;[4] and
- **H.R. 1165** (the Swift Approval, Full Evaluation (SAFE) Drug Act), introduced on February 16, 2007, by Representative Markey.

The bills and the IOM report address many of the same issues, often with similar approaches though at times with major differences. The IOM report addressed only drugs, not biological products (e.g., vaccines), in keeping with the charge FDA gave it. FDA's response to the IOM recommendations, therefore, relates to drugs, but also states that the approach to drug safety is relevant to all medical products. All the bills would amend the Federal Food, Drug, and Cosmetic Act (regarding the regulation of drugs); S. 484 would also amend the Public Health Service Act (regarding the regulation of biologics). Highlighted below are a few of the more significant items regarding drug safety.

FDA organization. S. 468/H.R. 788 would remove the post-approval drug safety activities from FDA's Center for Drug Evaluation and Research (CDER) and create a new Center for Postmarket Evaluation and Research for Drugs and Biologics (the Center). The IOM report does not suggest that approach to strengthen FDA's postmarket activities, nor do the other pending bills.

FDA authority to require action and to enforce compliance. The bills and the IOM recommendations aim to strengthen FDA's ability to make sure drug manufacturers (application sponsors) appropriately design and conduct postmarket studies and disclose the results to the public. S. 468/H.R. 788 lays out requirements that the new Center for Postmarket Evaluation and Research for Drugs and Biologics would administer; S. 484 would achieve this with a process it calls a Risk Evaluation and Mitigation Strategy (REMS); and H.R. 1165 would allow the Secretary to require certain studies. The IOM recommended and all the bills would allow the Secretary to penalize (through civil fines, injunctions, or withdrawal of marketing approval or

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[4] This report covers Title I (Risk Evaluation and Mitigation Strategies) of S. 484; it does not cover Title II (Reagan-Udall Institute for Applied Biomedical Research), Title III (Clinical Trials), or Title IV (Conflicts of Interest).

licensure) sponsors who do not conduct required studies or complete them on time, or who fail to report study results.

Comparative-effectiveness studies. The IOM report and the bills address the need for FDA authority to require pre- and postmarket studies. S. 468 alone would give FDA the authority to require that those studies compare a drug's safety and effectiveness with that of other drugs.

FDA funding. All three bills would require a variety of drug safety activities. They differ in how to fund them. S. 468 / H.R. 788 would authorize appropriations to carry out the bill's provisions; S. 484 would rely on user fees, expanding FDA's existing authority to use such fees; and H.R. 1165 does not address funding. The IOM committee not only recommended that Congress provide "substantially increased resources" to FDA, but noted that all its other recommendations could not be implemented without those resources.

Table 1, beginning on page 4, addresses the range of FDA drug safety activities that the IOM recommended, along with FDA's response, and activities that the bills would authorize or require. The table structure follows the 25 IOM recommendations within the five categories of organizational culture, science and expertise, regulation, communication, and resources.[5]

[5] CRS Report RL32797, *Drug Safety and Effectiveness: Issues and Action Options After FDA Approval*, by Susan Thaul, addresses many of the topics covered in the IOM report and the Senate bills. The IOM report also addressed clinical trial registration and results database requirements; a separate CRS Report RL32832, *Clinical Trials Reporting and Publication*, by Erin D. Williams, describes and discusses those recommendations.

Table 1. Comparison of Drug Safety Provisions in S. 468 / H.R. 788, S. 484, and H.R. 1165 in Relation to Recommendations in the Institute of Medicine September 2006 Report and the Food and Drug Administration's January 2007 Response

Institute of Medicine September 2006 report recommendations	FDA January 2007 response to IOM report	S. 468, Grassley-Dodd-Mikulski-Bingaman & H.R. 788, Tierney-Ramstad	S. 484, Enzi-Kennedy	H.R. 1165, Markey
Organizational culture				
3.1 The committee recommends that the FFDCA be amended to require that the **FDA Commissioner** currently appointed by the President with the advice and consent of the Senate also be appointed for a **six-year term of office**. The Commissioner should be an individual with appropriate expertise to head a science-based agency, demonstrated capacity to lead and inspire, and a proven commitment to public health, scientific integrity, transparency, and communication. The President may remove the Commissioner from office only for reasons of inefficiency, neglect of duty, or malfeasance in office.	Not directed to FDA.	No provision.	No provision.	No provision.
3.2 The committee recommends that an **external Management Advisory Board** be appointed by the Secretary of HHS [the Department of Health and Human Services] to advise the FDA Commissioner in shepherding CDER [the FDA Center for Drug Evaluation and Research] (and the agency as a whole) to implement and sustain the changes necessary **to transform the center's culture** — by improving morale and retention of professional staff, strengthening transparency, restoring credibility, and creating a culture of safety based upon a lifecycle approach to risk-benefit.	Engaging external consultants to help develop comprehensive strategy.	No new entity. Refers to required responsibilities of the FDA Drug Safety and Risk Management Advisory Committee, which it would transfer to the new Center for Postmarket Evaluation and Research for Drugs and Biologics.	No new entity. Refers to the FDA Drug Safety Oversight Board. [Note: FDA limits membership to federal employees although allowing members from outside of FDA.]	No provision.

Institute of Medicine September 2006 report recommendations	FDA January 2007 response to IOM report	S. 468, Grassley-Dodd-Mikulski-Bingaman & H.R. 788, Tierney-Ramstad	S. 484, Enzi-Kennedy	H.R. 1165, Markey
3.3 The committee recommends that the Secretary of HHS direct the FDA Commissioner and Director of CDER, with the assistance of the Management Advisory Board, to **develop a comprehensive strategy for sustained cultural change** that positions the agency to fulfill its mission, including protecting the health of the public.	[See response to recommendation 3.2.]	No comparable provision; however, a related provision would establish a Center for Postmarket Evaluation and Research for Drugs and Biologics (the new Center) as a separate entity within FDA (not an administrative office of the FDA Center for Drug Evaluation and Research (CDER) or the FDA Center for Biologics Evaluation and Research (CBER). Would also transfer the Office of Surveillance and Epidemiology (OSE, formerly called the Office of Drug Safety) from CDER to the new Center.	No provision.	No provision.
3.4 The committee recommends that CDER **appoint an OSE [Office of Surveillance and Epidemiology] staff member to each New Drug Application review team** and assign **joint authority to OND [CDER's Office of New Drugs] and OSE for postapproval regulatory actions related to safety**.	Initiated two pilot projects to evaluate models for involving OSE staff (1) in reviews and (2) more significantly, in postmarket decision making. Would also improve communication between OSE and OND and work to assess the impact and value of routinely including postmarket review staff on premarket review teams.	Would require the new Center Director to review all applications and supplements and associated analyses before approval. Authorizes the new Center to require postmarket studies concerning safety and effectiveness, including comparisons with other products, specifying date due; studies could use epidemiology or other observational designs, or databases.	No provision.	No provision.

Institute of Medicine September 2006 report recommendations	FDA January 2007 response to IOM report	S. 468, Grassley-Dodd-Mikulski-Bingaman & H.R. 788, Tierney-Ramstad	S. 484, Enzi-Kennedy	H.R. 1165, Markey
	Established an associate director of safety and a safety regulatory program manager in each CDER OND review division; began regular safety meetings between OSE and all OND review divisions. FDA's proposal for a reauthorized Prescription Drug User Fee Act (PDUFA), which it refers to as PDUFA IV, includes provisions to improve communication and coordination between OSE and OND, including an assessment of the value of including postmarket review staff on premarket review teams. Created new procedures around decision-making about requesting further studies and labeling changes. Creating a standard operating procedure for presenting postmarket safety issues to advisory committees.			

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3.5 To restore appropriate balance between the FDA's dual goals of speeding access to innovative drugs and ensuring drug safety over the product's lifecycle, the committee recommends that Congress should introduce **specific safety-related performance goals in the Prescription Drug User Fee Act IV** in 2007.	PDUFA IV proposal includes safety-related activities, including work toward identifying and assessing risk management and communication tools; exploration of benefits of adverse event reporting; acquisition and use of databases; develop guidance on pharmacoepidemiologic studies and on clinical hepatoxicity and enriched trial designs; and improve communication between OSE and OND.	No comparable provision; however, the bill would authorize appropriations for safety activities [see below].	Would extend the definition of the activities on which drug user fees may be used to include the review and implementation of the Risk Evaluation and Mitigation Strategy (REMS [see below]) and the review of safety information including adverse event reports.	No provision.
Science and expertise				
4.1 The committee recommends that in order to improve the generation of new safety signals and hypotheses, CDER (a) conduct a systematic, scientific **review of the AERS [FDA's Adverse Event Reporting System] system**, (b) identify and **implement changes** in key factors that could lead to a more efficient system, and (c) systematically **implement statistical-surveillance methods** on a regular and routine basis for the **automated** generation of new safety signals.	Began upgrading the Web-accessible Adverse Events Reporting System (AERS) II to add signal detection and tracking tools. Implementing electronic system across CDER offices to track postmarket safety issues. If PDUFA IV proposal is accepted, would seek outside research organizations to study how to maximize public health benefits of the collection and reporting of adverse events over a product's lifecycle.	Would not require systematic and scientific review, but would require that the new Center Director improve postmarket surveillance programs and activities.	No provision.	No provision.

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4.2 The committee recommends that in order to facilitate the formulation and testing of drug safety hypotheses, CDER (a) increase their intramural and extramural programs that **access and study data from large automated healthcare databases**, and (b) include in these programs **studies on drug utilization** patterns and **background incidence rates** for adverse events of interest, and (c) develop and implement **active surveillance** of specific drugs and diseases as needed in a variety of settings.	Would use PDUFA IV funds to acquire databases and hire staff to use them; conduct targeted postmarketing surveillance, study drug-class effects, and detect signals. Sponsoring public meeting to explore opportunities for linking private- and public-sector "postmarketing safety monitoring systems to create a virtual integrated, interoperable Nationwide medical product safety network." Would use PDUFA IV funds to develop guidance on conducting pharmacoepidemiologic studies using large healthcare data sets; would hold public workshop to identify best practices and issue guidance on such practices. Would develop guidance on clinical hepatoxicity and enriched trial designs to support the prevention of safety problems during drug development.	Would require that the new Center Director conduct postmarketing surveillance, using risk-benefit analyses, adverse event reports, and clinical and observational studies. Would require the new Center to contract with domestic and international patient databases (or require the drug sponsor to do so) to conduct epidemiologic and other observational studies.	No provision.	No provision.

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	Current data-sharing activities include agreements with the Agency for Healthcare Research and Quality and the Veterans Health Administration, and active monitoring and analysis of influenza vaccine safety. Developing (through the critical path initiatives) techniques for predictive toxicology, identifying drugs' cardiovascular risk, preventing drug-induced liver injury, using integrated information, using new tools to enhance blood safety, and enhancing the safety of gene therapy.			
4.3 The committee recommends that the Secretary of HHS, working with the Secretaries of Veterans Affairs and Defense, develop a **public-private partnership** with drug sponsors, public and private insurers, for-profit and not-for-profit health care provider organizations, consumer groups, and large pharmaceutical companies to prioritize, plan, and organize funding for **confirmatory drug safety and efficacy studies of public health importance**. Congress should **capitalize** the public share of this partnership.	Signed agreement with the Veterans Health Administration to share information and expertise regarding medical product safety, effectiveness, and patterns of use.	No provision.	No provision.	No provision.

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4.4 The committee recommends that CDER assure the performance of **timely and scientifically valid evaluations** (whether done internally or by industry sponsors) of Risk Minimization Action Plans (RiskMAPs).	PDUFA IV proposal includes work toward identifying risk management tools; assessment of selected Risk Minimization Action Plans, risk management and risk communication tools; annual systematic review and public discussion of selected programs and tools and dissemination of reports; and public workshops to get prioritization guidance from industry and others.	Would set procedure to require risk management activities when deemed necessary and would require action to ensure follow-up and completion of sponsor requirements.	Would require a sponsor to submit a proposed Risk Evaluation and Mitigation Strategy (REMS) as part of its application for drug approval or biologics licensure. REMS must include labeling, reports of studies and surveillance data, and a pharmacovigilance statement. Based on the estimated number of people who would take the drug, disease seriousness, expected duration of treatment, and availability of other treatments, the pharmacovigilance statement would provide an assessment of adequacy of REMS activities to assess serious risks, to identify unexpected serious risks of the drug and whether studies are necessary, and, if studies are necessary, to describe what observational and clinical studies are required.	No provision.

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			If the Secretary were to determine it necessary, the Secretary could require that the REMS include a sponsor-developed Medication Guide or patient package insert; a plan to communicate with health care providers, encouraging implementation of relevant REMS components; post-approval observational studies (that the applicant or the Secretary could conduct) or clinical trials, with target schedules for completion and reporting; and restrictions on advertising. Would require an assessment of an approved REMS annually for the first three years after initial approval/licensure and then at a frequency (including none) as specified in the REMS.	

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4.5 The committee recommends that CDER develop and continually improve a systematic approach to **risk-benefit analysis** for use throughout the FDA in the **preapproval and post-approval** settings.	Held workshop on quantitative benefit-risk assessment; exploring use of best practices and identification and testing of quantitative tools; have introduced training courses for medical reviewers. Created group of internal experts to develop quantitative methods for safety evaluation, develop and disseminate best practices of safety reviews during product development, and to provide consistency across review divisions. Initiated critical path initiatives [See response to recommendation 4.2 above] and a pilot program to systematically review safety profiles of new molecular entities (NMEs) [See 5.4 below]. Established program with the National Toxicology Program of the National Institute of Environmental Health Sciences to develop animal model to assess cancer risk associated with gene therapy.	Would require that the new Center conduct and use risk-benefit analysis, but would not require that FDA develop and improve a systematic approach.	Would require REMS to include consideration of scope of use, seriousness of the disease or condition that the drug is used to treat or prevent, seriousness of adverse events, and other available treatment. When concerned about a serious risk that may be related to the pharmacologic class of a drug, the Secretary could defer a REMS assessment while convening meetings of the public, advisory committees, or expert panels to discuss possible responses to that concern. Secretary may coordinate timetable to review efforts of international marketing authorities.	No provision.

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	Initiative underway to strengthen the safety evaluation process, including standardized methodologies, training and mentoring, workload prioritization, and management tools.			
4.6 The committee recommends that CDER **build internal epidemiologic and informatics capacity** in order to improve the postmarket assessment of drugs.	[See responses to recommendations 3.5 and 4.2 above.]	No provision.	No provision.	No provision.
4.7 The committee recommends that the Commissioner of FDA demonstrate commitment to building the agency's scientific research capacity by:				
a) Appointing a **Chief Scientist** in the office of the Commissioner with responsibility for overseeing, coordinating, and ensuring the quality and regulatory focus of the agency's intramural research programs.	Commissioner proposed creation of the Office of the Chief Medical Officer to oversee FDA scientific operations.	No comparable provision, but the bill would create a separate Center for Postmarket Evaluation and Research for Drugs and Biologics (the new Center) and the position of Director of the new Center.	No provision.	No provision.
b) Designating the FDA's **Science Board** as the extramural advisory committee to the Chief Scientist.	Asked the FDA Science Board to review scientific needs and activities across FDA; engaging external consultants to help develop comprehensive strategy to improve organizational culture.	No provision.	No provision.	No provision.
c) Including **research capacity** in the agency's mission statement.	Not addressed.	No provision.	No provision.	No provision.

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d) Applying resources to **support intramural research** approved by the Chief Scientist.	Not addressed.	Would require that the new Center conduct postmarket risk assessments.	No provision.	No provision.
e) Ensuring that **adequate funding** to support the intramural research program is requested in the agency's annual budget request to Congress.	Not addressed.	Would authorize appropriations [see below].	Would allow for user-fee revenue to be used for REMS evaluation activities.	No provision.
4.8 The committee recommends that FDA have its **advisory committees review all NMEs [new molecular entities]** either prior to approval or soon after approval **to advise in the process of ensuring drug safety and efficacy or managing drug risks**.	Conducting pilot program to review new molecular entities [See response to recommendation 5.4 below].	No comparable provision, but the bill would require preapproval review by the new Center, and would require advisory committee consultation before the new Center Director makes a safety determination or orders a corrective action.	Secretary may convene an advisory committee meeting to review safety concerns or a REMS for a drug or a class of drugs.	No provision.
4.9 The committee recommends that all FDA drug product advisory committees, and any other peer review effort such as mentioned above for CDER-reviewed product safety, include a **pharmacoepidemiologist** or an individual with comparable public health expertise in studying the safety of medical products.	Will increase (to the extent feasible) pharmacoepidemiology experts support to advisory committees.	No provision.	No provision.	Would require HHS Secretary to allow FDA staff to present information to an advisory committee if staff is working on a topic the committee is considering.
4.10 The committee recommends FDA establish a requirement that a substantial majority of the members of each advisory committee be **free of significant financial involvement with companies** whose interests may be affected by the committee's deliberations.	Will issue new guidances to address the granting and disclosure of conflict-of-interest waivers for advisory committee members, and to improve the release of advisory committee briefing materials to the public. Will make advisory committee member recruitment more transparent by issuing lists of vacancies.	No provision.	No provision in Title I; related provisions are in Title IV ("Conflicts of Interest").	No provision.

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4.11 To ensure that **trial registration** is mandatory, systematic, standardized, and complete, and that the registration site is able to accommodate the reporting of trial results, the committee recommends that Congress require industry sponsors to register in a timely manner at *clinicaltrials.gov*, at a minimum, **all Phase 2 through 4 clinical trials**, wherever they may have been conducted, **if data from the trials are intended to be submitted to the FDA as part of an NDA [new drug application], sNDA [supplemental new drug application], or to fulfill a postmarket commitment**. The committee further recommends that this requirement include the **posting of a structured field summary of the efficacy and safety results** of the studies.	Not directed to FDA.	[Note: Senators Dodd and Grassley introduced a separate bill (S. 467) that addresses the issues of clinical trial registration and results databases. The comparison of that bill to Title III of S. 484 and the IOM report recommendations appears in a separate CRS product: CRS Report RL32832, *Clinical Trials Reporting and Publication*, by Erin D. Williams.]		No provision.
4.12 The committee recommends that FDA **post all NDA review packages on the agency's website**.	Not accepted.	Would require that FDA post all studies required under the preapproval and postapproval requirements of this section.	Would require that FDA post all approved professional labeling and any required patient labeling in a searchable electronic repository.	Would require, within 24 hours of approval, that the Secretary publish a summary statement of the scientific basis for the approval and how the decision balanced risks and benefits. The statement must include a description of controversies and differences of opinion within FDA and their resolutions, and include any statement submitted for the summary by involved staff.

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4.13 The committee recommends that CBER review teams regularly and systematically **analyze all postmarket study results** and **make public** their assessment of the significance of the results with regard to the integration of risk and benefit information.	Decisions to publicly disclose assessments of postmarketing safety studies must be made on a case-by-case basis. Will publish newsletter on FDA website, summarizing results and methods of postmarket reviews, and providing information on emerging safety issues and on recently approved products. Will issue final guidance on communicating important drug safety information to healthcare professionals, patients, and other consumers.	Would require that FDA publish in the Federal Register and post on the Internet drug safety and effectiveness information.	Would require that the drug sponsor submit REMS assessments at least annually for the three years after approval/licensure; after that at increased or reduced (including none) frequency as the Secretary determines to be necessary. Would set time limits for the Secretary to act on initial REMS and modification requests. A dispute resolution process would include timeframes, and involve review by and recommendations of the Drug Safety Oversight Board (with added expertise, if necessary, from the FDA offices of Pediatrics, Women's Health, and Rare Diseases).	Would require biennial reports on approved applications supported by noninferiority studies, and biannual reports regarding postmarket studies. Would prohibit directing FDA staff to distort or suppress scientific research, analysis, opinion, or recommendations or to wilfully disclose scientific information that is false, misleading, or incomplete. Would provide for disciplinary actions and would require annual Inspector General reports. Would also provide whistleblower protection (with provisions for enforcement and penalities) and the right to publish.

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Regulation				
5.1 The committee recommends that Congress ensure that the Food and Drug Administration has **the ability to require such postmarketing risk assessment and risk management programs as are needed to monitor and ensure safe use** of drug products. These conditions may be imposed both **before and after approval** of a new molecular entity, new indication, or new dosage, as well as **after identification of new** contraindications or patterns of adverse events. The limitations imposed should match the specific safety concerns and benefits presented by the drug product. The risk assessment and risk management program may include:	Not directed to FDA.	Would authorize FDA to require safety and effectiveness studies, including in comparison to other drugs/biologics, according to FDA-specified timetable and terms, if, at any time, the new Center Director determines the need. Would authorize FDA to require limitations on the distribution of a drug or biologic. These include:	Would require that the drug sponsor submit a REMS for each new drug and biologic, for a generic drug (all information except postapproval clinical trials), for a new indication (either for a drug with a current REMS or a drug without a REMS when a prescription is required for its dispensing), and for new safety information. Would allow a sponsor to submit a REMS assessment at any time. Would authorize the Secretary to require a REMS assessment at any time the Secretary determines that new safety information requires review. Would require that restrictions be commensurate with the risks; necessary; and not unduly burdensome on patient access to drugs. Would authorize FDA to require limitations on a product's distribution. These include:	Would authorize the Secretary, after providing public notice, to order the sponsor to conduct studies to address safety or effectiveness issues identified after approval/licensure. Would allow the following restrictions on distribution or use during study if Secretary determines it necessary to ensure safety and effectiveness (Secretary may order the restrictions continued, terminated, or changed based on study results):

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a) Distribution conditioned on **compliance with agency-initiated changes in drug labels**.		changes in labeling;	changes in labeling;	
b) Distribution conditioned on specific **warnings to be incorporated into all promotional materials** (including broadcast DTC [direct-to-consumer] advertising).		statements in advertisements;	disclosure in advertisements that the available information may not allow for full assessment of serious risks; or, if the Secretary determines it necessary, statement in advertisements regarding risk or use information included in the label.	
c) Distribution conditioned on a moratorium on **direct to consumer advertising**.		FDA (the new Center) review of advertisements before they are released;	FDA review of advertisements before they are released;	restrictions on DTC advertising;
d) Distribution **restricted to certain facilities, pharmacists, or physicians** with special training or experience.		patient or physician education;	training, experience, or certification of healthcare providers, pharmacists, and care setting, or use only in certain settings; a compliance system with restrictions on providers, pharmacists, patients, and others who fail to meet requirements;	certain facilities or physician training or experience;
e) Distribution conditioned on the performance of **specified medical procedures** [e.g., requiring a pregnancy test if a drug might cause abnormal fetal development].			documentation of safe-use conditions, such as laboratory test results;	performance of specified medical procedures;

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f) Distribution conditioned on the performance of **specified additional clinical trials or other studies**.		the establishment of a risk management plan;	a new post-approval study or changes in the design of an ongoing study, that FDA could request at the time of approval/licensure or any time afterward;	
g) Distribution conditioned on the maintenance of an **active adverse event surveillance system**.		a patient registry;	a patient registry or patient monitoring;	
		patients to sign a consent form;		
		modification of indication;	modification of indication.	
		the monitoring of sales and usage.		
				For a drug approved pursuant to accelerated approval:
				would require, as a condition of approval, that the sponsor submit and the Secretary approve protocols for postmarket studies, including timeframe and milestones. Until the study commitments are completed, Secretary must require restrictions on distribution and use;

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				would also require a statement on labeling that the drug received accelerated approval and that required studies are underway; to include a list of issues being addressed; and labeling to state that FDA gave conditional approval under its accelerated approval process; and that the drug will not receive full approval until completion of studies; would require that the Secretary amend 21CFR314 to require a public meeting if postmarket studies after accelerated approval are not completed within two years; and would require, for a drug approved based on animal efficacy data, studies when ethical and feasible to verify and describe clincial benefit, safety and effectiveness. If a completed study is inconclusive (or not completed within five years), the Secretary would withdraw product from commercial distribution, limiting its availability and requiring informed consent.

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5.2 The committee recommends that **Congress provide oversight and enact any needed legislation** to ensure compliance by both the FDA and drug sponsors with the provisions listed above. FDA needs **increased enforcement authority** and **better enforcement tools** directed at drug sponsors, which should include fines, injunctions, and withdrawal of drug approval.	Not directed to FDA.	If a sponsor were to fail to complete required studies or comply with ordered corrective action, would authorize FDA to require civil monetary fines of $250,000 for the first 30-day period, doubling for every subsequent 30-day period (not to exceed $2 million for any 30-day period); changed promotion; and withdrawal of product approval or licensure. If the new Center Director determined that a product may present an unreasonable risk that cannot be satisfactorily alleviated by a corrective action or if a drug's sponsor fails to comply with an order or requirement, the new Center Director, after consultation with the Director of CBER or CBER, could withdraw or suspend the product's approval/licensure.	Would authorize civil money penalties of $15,000 — $250,000 per violation (not to exceed $1 million within one adjudicated proceeding) for failure to comply with an approved REMS. Would consider a drug misbranded if it failed to comply with the Secretary's requirements to change labeling or regarding advertising. [Note: Authority for approval/licensure withdrawal already exists in law.]	Would consider a drug misbranded if it failed to comply with postmarket study or distribution requirements, or label change orders. Would authorize civil penalties of not more than 100% (300% if violation caused a consumer harm) of sponsor's gross profits from sales of the drug, or $1 million ($3 million if consumer harmed), whichever is greater. Would authorize the same penalities for failure to act with "due diligence" to complete postmarket studies required based on applications for a fast track product or accelerated approval of a new drug for a serious or life-threatening illness. Would also consider a drug to be misbranded if a manufacturer failed to comply with the Secretary's order to make specific label changes to ensure safe and effective use of the drug.

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		The Secretary would have to publish in the Federal Register and post on the Internet details regarding reason, factual basis, and reference to supporting empirical data, for determination; explanation that describes why contrary data are insufficient; and position taken by each individual consulted.		
5.3 The committee recommends that Congress amend the FFDCA to require that **product labels carry a special symbol** such as the black triangle used in the UK or an equivalent symbol **for new drugs**, **new combinations** of active substances, and **new systems of delivery** of existing drugs. The FDA should **restrict direct-to-consumer advertising** during the period of time the special symbol is in effect.	Not directed to FDA.	Does not specify special symbol. Would authorize FDA, for two years after initial approval/licensure and for all drugs with outstanding required studies, to require preapproval submission of promotional material, and to require a statement that the product is new.	Does not specify special symbol, but allows FDA to require statement in ads. [Note: As of January 2006, FDA requires date of approval but not a symbol on label.] May require submission of advertisements to FDA for preclearance; specific disclosures in advertisements, which may include approval date, statement that "existing information may not have identified or fully assessed all serious risks of using the drug," serious adverse events listed in drug's labeling, or "protocol to ensure safe use described in the labeling of the drug...."	For drugs approved under accelerated approval procedures, would require a statement on labeling that the drug received accelerated approval and that required studies are underway, and to include a list of issues being addressed. Would also require labeling to state that FDA gave conditional approval under its accelerated approval process; and that the drug will not receive full approval until completion of studies.

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			May require temporary moratorium on direct-to-consumer advertisements for up to two years after initial approval if Secretary determines other required disclosure is inadequate to protect public health and safety, and that such prohibition is necessary while additional information is collected, considering expected scope of use, alternatives, and the extent to which studies used to approve the drug may not have identified serious risks.	
5.4 The committee recommends that **FDA evaluate all new data on new molecular entities no later than five years after approval**. Sponsors will submit a report of accumulated data relevant to drug safety and efficacy, including any additional data published in a peer reviewed journal, and will report on the status of any applicable conditions imposed on the distribution of the drug called for at or after the time of approval.	Conducting pilot developed by OSE and OND to review systematically the safety profiles of new molecular entities on a regularly scheduled basis to determine whether these reviews should be initiated for all NMEs. Will incorporate AERS data, data mining analysis, epidemiologic data, postmarketing clinical trial information, and a review of the Periodic Safety Update Reports (U.S. Periodic Reports) to identify potential safety concerns early in the product life cycle.	No provision.	No provision.	No provision.

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Communication				
6.1 The committee recommends that Congress enact legislation establishing a new FDA **advisory committee on communication with patients and consumers**. The committee would be composed of members who represent consumer and patient perspectives and organizations. The advisory committee would advise CBER and other FDA centers on communication issues related to efficacy, safety, and use during the lifecycle of drugs and other medical products, and it would support the centers in their mission to "help the public get the accurate, science-based information they need to use medicines and foods to improve their health."	Establishing a new advisory committee regarding FDA's communication policies and practices; members will include patients and consumers and experts in risk and crisis communication and social and cognitive sciences.	No provision.	No provision.	No provision.

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6.2 The committee recommends that the **new Office of Drug Safety Policy and Communication should develop a cohesive risk communication plan** that includes, at a minimum, a review of all Center risk communication activities, evaluation and revision of communication tools for clarity and consistency, and priority-setting to ensure efficient use of resources.	Established a working group to develop a CBER risk communication strategic plan. Doing so will explore communication tools, and evaluate and improve the CBER website. Established the Bioinformatics Board in the Office of the Commissioner to improve the public's ability to communicate with FDA, including adverse event reports and consumer complaints.	Would require that FDA make safety issues public via the Federal Register and Internet, but does not require development of a plan. Would require that, not less than every 90 days, the Secretary publish in the Federal Register: information about required studies to include type, nature, outcomes, date required by FDA or agreed to by sponsor, date for completion, and reason that any study was not completed by deadline; progress reports and results of completed studies; and explanations of the new Center Director's determinations, if any.	Would authorize FDA to require a MedGuide or patient package insert, and a communication plan to providers. Would require that the Secretary, within one year, submit to congress an assessment of the information technology (IT) infrastructure (data collection and data mining systems, and external database and personnel assets and training programs) that FDA would need to: conduct the activities that this bill would require; achieve interoperability among FDA Centers and product sponsors; and use electronic health records. Also required would be an assessment of whether those assets were sufficient, a plan for enhancing FDA's IT assets, and an assessment of what additional resources FDA would need to make those IT enhancements.	No provision.

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		Would require the HHS Secretary, in consultation with the FDA Commissioner and the Directors of the new Center and CDRH, to submit a report to Congress about current postmarket surveillance of FDA-approved medical devices that identifies gaps, recommends ways to improve them, and identifies changes in authority needed to make those improvements, recognizing the legitimate differences between devices and other medical products.	Would require that the Secretary, through FDA and the National Institutes of Health, establish a publicly available, searchable repository of structured, electronic product information; and report progress annually to Congress.	
Resources				
7.1 To support improvements in **drug safety and efficacy activities over a product's lifecycle**, the committee recommends that the Administration should request and Congress should approve substantially **increased resources in both funds and personnel** for the FDA.	Notes that PDUFA IV funds, which require congressional action, would not be sufficient to fully implement the IOM recommendations.	Would authorize appropriations (beginning with $50 million in FY2008, going to $150 million in FY2012) to carry out this bill's provisions.	Would authorize the use of PDUFA fees for safety activities specified in this bill; would amend the PDUFA provisions [21 USC 379(c)(2)] to include directions for the Secretary's calculation of workload adjustments for annual adjustments to fees.	No provision.