A New Phase of Pharmaceutical Regulation

Amidst criticism of the FDA’s handling of drug safety issues, continued controversy and litigation over claimed hazards of important drugs, and a split in the courts over whether product liability claims against drug and medical device manufacturers are preempted by federal law, Congress enacted and President Bush signed into law the most extensive revision of the Federal Food, Drug, and Cosmetic Act (FDCA) in a decade: The Food and Drug Administration Amendments Act, Pub. L. No. 110-85, 121 Stat. 823 (2007) (FDAAA) (usually pronounced “fuh-dah-aah”). Some have hailed FDAAA as important reform legislation that will greatly improve the safety and effectiveness of drugs and medical devices and restore “lost luster” to the FDA. Others lament the statute’s length and complexity and question its likely impact. Important officials at the FDA have called it “sweeping,” “ground-breaking,” and “a very significant addition to FDA authority,” while conceding it will take years to understand what it means and to implement its changes. For most lawyers litigating drug and medical device cases, it remains an enigma. What is FDAAA, and what will it mean for the future of drug and device product liability litigation?

Overview
FDAAA represents a new phase of pharmaceutical regulation, an evolution of the philosophy and mechanics of drug safety. It is a “coming of age” of therapeutics, says Dr. Janet Woodcock, Deputy Commissioner of the FDA and Director of the FDA’s Center for Drug Evaluation and Research, made necessary by the overall ubiquity of medicines in our society.

The FDA traditionally has balanced a drug’s benefits against its risks at the time of approval, and approved as safe and effective those drugs whose demonstrated benefits to the intended patient population are expected to exceed the drug’s risks, when the drug is used according to its approved labeling.

But sometimes unanticipated safety and efficacy issues arise after a drug is approved and on the market. Sometimes problems appear only after longer-term use than was studied in the pre-approval clinical trials, because physicians use the...
drug in different patient populations or for different indications than were studied pre-approval, or because the drug interacts with other medicines in unforeseen ways, or for any number of other unanticipated reasons. The FDA may become aware of new safety issues in various ways. For example, the FDA receives and monitors spontaneous adverse event reports, which may signal the possibility of a problem with a drug. Manufacturers sometimes conduct additional post-market studies and clinical trials. Sometimes post-market studies or clinical trials are undertaken as a condition of approval, and often they are initiated to obtain approval for a new indication or use for the drug. The results are submitted to the FDA, which reviews them, along with the results of studies and clinical trials conducted by academics. Occasionally the FDA itself queries existing patient databases to obtain additional information about a drug’s performance. But the FDA has not generally conducted or required systematic post-approval studies of a drug’s performance in large patient populations.

FDAAA envisions a very different approach to detecting post-approval safety issues. It mandates that the FDA investigate whether there are valid ways to engage in active surveillance of combinations of large patient databases, in an effort to ferret out signals of potential problems at an earlier date. If so, the FDA must engage in active surveillance and report any drug safety signals it detects.

Problems with drug safety also arise because the health care delivery system in this country—which is not regulated by the FDA—is imperfect. Doctors and other health care providers serving as learned intermediaries are expected to become familiar with the drug’s properties by reading the label, and through other sources, and to make appropriate risk/benefit decisions for their individual patients. But prescribers sometimes fail to read or comply with label requirements, or they make other mistakes. Patients sometimes abuse drugs. And other shortcomings can conspire to create unexpected drug hazards. In recent years the FDA has sought to deal with these and similar problems by restricting the distribution of certain drugs. FDAAA codifies the FDA’s efforts to minimize post-approval risks by authorizing the FDA to impose Risk Evaluation and Mitigation Strategies (REMS) on new and previously approved drugs. If a new safety issue cannot be resolved by imposing a REMS, or if the active surveillance system raises unanswered questions, FDAAA also authorizes the FDA to order drug manufacturers to conduct additional studies and clinical trials. Finally, it expressly authorizes the FDA to make post-approval label changes in response to new safety data.

FDAAA consists of 11 separate titles covering a broad array of topics:

- Titles I and II reauthorize for four years drug and medical device user fee statutes, respectively, which were set to expire at the end of 2007.
- Titles III through V reauthorize pediatric drug and medical device legislation. They also create new incentives for medical device manufacturers to develop devices for children, and provide the FDA with additional authority to review and regulate those devices.
- Title VI creates the Reagan-Udall Foundation, a private-public collaboration aimed at serving unmet scientific needs in the regulation of drugs and medical devices. Title VII addresses advisory committee conflicts of interest, and Title VIII provides for a significant expansion of the clinical trials registry database.
- Title IX outlines the most significant new initiatives founded by FDAAA, which are intended to improve the post-market safety of drugs. Among other things, Title IX directs the FDA to study, and if possible, engage in active surveillance of large, electronically linked databases in an effort to uncover drug safety signals more quickly. It also allows the FDA to impose REMS, and explicitly authorizes the FDA to require post-approval studies, clinical trials, and labeling changes.
- Title X addresses food and pet food safety.
- Title XI contains a number of miscellaneous provisions.

Many of FDAAA’s provisions are unclear, and their meaning no doubt will be fleshed out by regulation and litigation. The sparse legislative history sheds little light on the new law’s meaning. When the bill that became FDAAA finally passed in late September 2007, the FDA’s preexisting authority to assess user fees for reviewing new drug applications was due to expire within a matter of days, and the agency was on the verge of furloughing hundreds of staffers for lack of funds. This made FDAAA “must-pass” legislation and may help explain the overwhelming majorities it garnered in both the House and Senate. It may also account for the paucity of legislative history. Although there is a House Report on H.R. 2900, the predecessor to H.R. 3580 (the bill that was enacted), no conference report was published. And the floor debate in both chambers sheds little light on the statute’s meaning.

This article looks at the provisions of FDAAA most likely to influence product liability claims against drug and medical device manufacturers and assesses their likely impact.

**Title I: Prescription Drug User Fee Amendments of 2007**

Title I of FDAAA reauthorizes the Prescription Drug User Fee Act (PDUFA), which had been set to expire September 30, 2007, through fiscal year 2012. First enacted in 1992, PDUFA’s purpose is to generate revenue by charging user fees in exchange for expedited review by the FDA of certain new drug applications. The new provisions allow the FDA to increase user fees to approximately $400 million annually. FDAAA §103(b). The fees will be adjusted upward to reflect inflation and increases in the FDA’s workload. User fees are expected to account for about one-quarter of the FDA’s annual operating budget. FDAAA also allows the FDA to collect an additional $225 million in user fees for drug safety activities over the next four years. *Id.*

Adequate funding is necessary for a strong and effective FDA. For consumers, adequate funding will mean that the FDA should be able to approve innovative...
new drugs and devices more expeditiously, thereby improving quality of life, reducing suffering, and saving lives. Together with the new drug safety provisions of Title IX, additional funding may also allow the FDA to better identify drug safety issues, and resolve them more effectively.

For the drug and medical device industry, a strong and effective FDA helps in a number of ways. First, prompt review of new drug and device applications allows manufacturers to get their products to the market more quickly. Second, as discussed more fully below, additional funding and the drug safety provisions of Title IX should allow the FDA to work with drug companies to identify safety concerns more quickly and to resolve them with more measured approaches that will not unduly alarm the public or result in unwarranted withdrawal of drugs from the market. Third, regardless of the U.S. Supreme Court’s decision in the upcoming Wyeth v. Levine preemption case, if the industry is to have any hope that Congress will allow (or continue to allow) federal law to preempt state-law tort claims by those who contend they were injured by FDA-approved drugs or medical devices, the FDA must do its job well. After all, the primary policy basis for choosing to preempt state law claims is that the country is better off having the experts at the FDA—rather than lay juries—determine whether the benefits of a drug or medical device outweigh its risk of harm. To use Justice Scalia’s language in Riegel v. Medtronic, Inc., “the solicitude for those injured by FDA-approved devices” and drugs must be “overcome in Congress’ estimation by solicitude for those who would suffer without new medical devices” and drugs “if juries were allowed to apply the tort law of 50 States to all innovations” and new drugs. 128 S. Ct. 999, 1009 (2008). Neither Congress nor the public would have any appetite for preemption if the FDA were severely weakened by underfunding.

Finally, a strong and well-funded FDA is essential to those lawyers who defend product liability claims brought against drug and medical device manufacturers. In each case, assuming the claim is not preempted, the jury must be made to respect the FDA's determination that the drug or device is “safe and effective,” and dissuaded from reaching a different conclusion. That becomes a difficult sell if the FDA is perceived as underfunded and ineffectual.

Although the goal of adequate FDA funding is almost universally recognized as laudable, PDUFA’s quid pro quo of user fees in exchange for expedited review by the FDA has attracted some criticism. A study released earlier this year, which was coauthored by a long-time critic of the FDA and ally of the plaintiffs’ bar, asserts that drugs approved near the FDA’s deadline for expedited review had a significantly higher rate of post-market safety problems and concludes that the expedited approval process may allow more unsafe drugs on the market. See Daniel Carpenter, Evan James Zucker, and Jerry Avorn, “Drug-Review Deadlines and Safety Problems,” 358 New Eng. J. Med. 1354 (2008). The FDA has disputed both the study’s conclusions and the data cited to support them. “FDA won’t approve a drug if we are not ready,” the FDA’s Dr. Janet Woodcock has said. See Keith J. Winstein, “Late Approval of Drugs Linked to Safety Issues,” The Wall Street Journal, March 27, 2008. Conversely, Dr. Woodcock has noted the need to get lifesaving drugs approved more quickly, and several studies support the agency’s position that expedited review saves lives. Under current guidelines, the agency attempts to reach a decision on 90 percent of new drug applications within 10 months of submission, and for priority drugs, within six months. PDUFA IV Performance Goals at I(A), available at [http://www.fda.gov/oc/pdufa4/pdufa4goals.htm](http://www.fda.gov/oc/pdufa4/pdufa4goals.htm). The debate on user fees for expedited review is likely to continue. It also may be a factor in product liability cases involving drugs given expedited review.

Unfortunately, as the FDA has itself noted, it may be some time before all of FDAAA’s user fee increases can be put to work. First, not all of the increased funds have been appropriated. Second, less-than-competitive salary levels, competition from other employers, and a “very dysfunctional” hiring system have left many FDA staff positions unfilled, according to Office of New Drugs Director John Jenkins. “FDA’s ‘Dysfunctional’ Hiring System May Be Good For Drug Safety Databases,” 70 The Pink Sheet, No. 9, p. 3 (March 3, 2008). Earlier this year, Dr. Woodcock told Congress that the Center for Drug Evaluation and Research was understaffed by 550 employees. Id. The FDA is having a particularly hard time attracting epidemiologists, she noted. Id. At least in the short term, the FDA is using funds that would otherwise go to payroll to fund some of the drug safety initiatives discussed below. Id. The problem should be only temporary, as the FDA has streamlined its hiring process and has begun hiring in earnest. See K. Rawson, “CDER Hiring Frenzy: More Reviewers Means Faster Reviews,” The RPM Report (June 8, 2008).

FDAAA also created a new §736A of the FDA, for the first time authorizing the FDA to collect user fees from manufacturers that voluntarily request the FDA to provide pre-dissemination advisory reviews of direct-to-consumer (DTC) television advertisements. FDAAA §104. Many companies view such reviews as advantageous because they provide FDA input on whether the advertisements are accurate, balanced, and adequately supported in compliance with FDA requirements before dissemination to the public. The new fees were intended to help pay the salaries of additional FDA employees who would engage in the review. However, FDAAA provided that the DTC user fee program would not commence if the FDA failed to receive at least $11.25 million to fund the program from a combination of user fees and congressional appropriations by January 25, 2008. Industry response was generally positive, and it looked like the FDA would receive sufficient user fees to get the program underway. Congress, however, failed to appropriate suffi-
cient funds, and the program was scrubbed for fiscal year 2008. See 73 Fed. Reg. 2924 (Jan. 16, 2008). The program could still be implemented in 2009 if Congress appropriates sufficient funds.

In connection with PDUFA Reauthorization, the FDA committed to what are known as the PDUFA IV Performance Goals. Available at http://www.fda.gov/oc/pdufa4/pdufa4goals.htm. For the most part, these goals are only slightly changed from those established at the time of the last PDUFA reauthorization. But the PDUFA IV performance goals include important new commitments in the area of drug safety and pharmacovigilance. Other new performance goals relate to the FDA’s review of proprietary drug names.

Title II: Medical Device User Fee Amendments of 2007
Title II of FDAAA reauthorizes the fees established under the Medical Device User Fee and Modernization Act (MDUFMA), which was first enacted in 2002, through fiscal year 2012. FDAAA reduces certain pre-market approval application and §510(k) fees but also creates three new types of fees: (1) an annual establishment registration fee; (2) an annual fee for filing certain periodic reports required by a pre-market application approval order; and (3) a 30-day notice fee that is limited to a request to make modifications to manufacturing procedures or methods affecting the safety or effectiveness of a device. Again, the most significant aspect of Title II in terms of its impact on future product liability cases is that it improves FDA funding. The idea behind the new fee structure is that it will provide a more stable and predictable source of revenue for the FDA, increase overall funding, and reduce the fee burden on smaller manufacturers.

Title II contains several other provisions. The one most likely to affect future product liability cases is a provision requiring the FDA to promulgate regulations to establish a device identification system. These regulations must require that medical devices include a unique identifier in their labeling that is specific enough to identify the device through distribution and use. FDAAA §226(a)(2). FDAAA requires a similar identifier for prescription drugs. Id. §913.

Title III–V: Pediatric Drugs and Medical Devices
Title III through V of FDAAA relate to drugs and medical devices for children. Although these portions of FDAAA contain important new provisions, their impact on product liability cases will likely be confined to those involving children.

The provisions that relate most closely to product liability concern post-market surveillance. Among other things, Title III expands the types of devices for which the FDA may require post-market surveillance to include any device “expected to have significant use in pediatric populations.” This provision allows the FDA to order post-market surveillance even on devices not approved for use in children but that are expected to be used in pediatric patients.

Product liability cases involving children also may be affected by new labeling provisions contained in Title IV. The new law provides that the FDA “shall order the label of a product” to include pediatric study information about whether the study demonstrates safety or efficacy in children, or whether the assessment results are inconclusive. FDAAA §402. Manufacturers that make labeling changes are required to distribute the relevant information to physicians and health care providers.

Title VI: Reagan-Udall Foundation
Title VI of FDAAA establishes the Reagan-Udall Foundation, a nonprofit corporation whose purpose is to advance the FDA’s “Critical Path Initiative”—an effort to modernize the scientific process through which a potential drug, biologic, or medical device is transformed into a medical product—and more broadly to advance the science needed for effective regulation of drugs and devices. The foundation’s primary duties are to identify unmet needs in the sciences of developing, manufacturing, and evaluating the safety and effectiveness of diagnostics, biologics, devices, and drugs. In addition to creating the foundation, Title VI authorizes the FDA to enter into collaborative agreements with private entities, such as academic institutions and nonprofit organizations with expertise in biomedical science, to implement the Critical Path Initiative.

Title VI engendered some controversy. Critics feared that the industry would use the foundation to co-opt the FDA. But the FDA is glad to have the foundation, and it intends to impose firewalls to ensure that the same staff involved in foundation projects will not decide regulatory issues concerning those projects. More important, FDA officials recognize that the standards they impose to regulate food, drugs and devices must be well-grounded in science. For example, how much of a particular pesticide should be permitted in a certain food? That particular regulatory standard—and many others—require applied research that the FDA does not believe is currently adequate. Similar issues arise concerning how to test, evaluate, and regulate biologics and emerging fields such as nanotechnology. Through the foundation, FDA officials hope to work with industry to get the scientific work in these areas done, both because the FDA has insufficient resources to do it alone and because involving industry is likely to yield more useful and accurate outcomes.

FDA officials also bemoan the scarcity of advanced academic programs in critical areas such as pharmaceutical manufacturing and the management of clinical trials. They hope that further study in these areas will improve safety and reduce uncertainty, and that the foundation will someday have a robust fellowship program.

Title VII: Advisory Committee Conflicts of Interest
Many lawyers defending drug and medical device product liability cases like to highlight favorable decisions by FDA advisory committees. For example, if an advisory committee has agreed on the content of a drug’s label, and the trial judge overrules evidentiary objections, the jury may be told that a panel of experts assembled by the FDA agreed that the label was appropriate.

In response, plaintiffs’ lawyers have sometimes attempted to undermine the credibility of FDA advisory committees by pointing to individual member’s industry ties. If the trial judge allows this tactic (something we do not endorse), conflict of interest standards governing advisory committee membership may come into play. Not surprisingly, many of the most knowledgeable experts in any given field come from industry or conduct research sponsored by industry. Having those experts participate on advisory committees is extremely beneficial to the FDA and the public. Even before FDAAA, the FDA
issued draft guidance on conflicts of interest, providing generally that the FDA may waive conflicts of interest that might otherwise impede qualified physicians and scientists from serving on advisory committees. See Draft Guidance for the Public, FDA Advisory Committee Members, and FDA Staff on Procedures for Determining Conflict of Interest and Eligibility for Participation in FDA Advisory Committees, available at http://www.fda.gov/oc/advisory/waiver/CO1guidef11.htm.

Title VII of FDAAA acknowledges the FDA’s need to grant advisory committee conflict of interest waivers where necessary to obtain essential expertise, but at the same time imposes limits on the number of waivers the FDA may grant. FDAAA §701. The new law requires the FDA to determine the aggregate percentage of waivers provided in fiscal year 2007, and compels the FDA to reduce the number of waivers by five percent each fiscal year through 2012 for a total 25 percent reduction over the next five years. The FDA must disclose any waivers on its website no later than 15 days before a scheduled advisory committee meeting. It must also report to Congress on the number of advisory committee vacancies and nominations, the number of disclosures required, and a plan detailing how the FDA plans to reduce the number of vacancies.

Title VIII: Clinical Trial Databases
When Congress first mandated the establishment of the existing clinical trials registry through section 113 of the Food and Drug Administration Modernization Act of 1997, the purpose was to provide a means to alert patients with severe and life-threatening diseases—and their doctors—to the availability of clinical trials. Title VIII of FDAAA provides for a significant expansion of the current clinical trial registry database (ClinicalTrials.gov). Previously, the only information listed in the clinical trials database was information about clinical trials conducted under the FDA’s Investigational New Drug Application process regulations that were intended to treat serious or life-threatening diseases or conditions. The expanded database will include trials for all diseases and conditions. Title VIII also expands the information available about the trials, and it adds clinical trials of medical devices. The vision is that the database will be searchable by keywords, safety issues, and at least one of the following: the disease or condition, name of the drug or device, location, age group, study phase, sponsor, recruitment status, or identification number. FDAAA §801(a)(2).

Title VIII also embraces an entirely new purpose: to compel early and complete public disclosure of clinical trial results. And it is in this area that it ties in most directly to product liability cases, because the upshot is that important clinical trial results that might not otherwise have been easily available—or available at all—will now appear on a public database. For example, otherwise unpublished clinical trial information on competitor drugs might be available.

More specifically, FDAAA requires the establishment of a new database that will include the results, including adverse events, of all trials that form the primary basis of an efficacy claim or that are conducted after a drug or a device is approved. By September 27, 2008, the results database must include: the demographic and baseline characteristics of the subjects who participated in the study, primary and secondary outcomes (including statistical results), contact information for inquiries about scientific information relating to the study, and a statement about whether an agreement exists that restricts the ability of the principal investigator to discuss or publish the results of the study.

The results database must include clinical trials for all approved products, and the FDA is required to determine through regulations whether to also include trials for unapproved products. The FDA must also determine the timeline and format for submission of results and updates, procedures for quality control, and the best method for reporting adverse event information in a way that is not misleading to patients or doctors. Additionally, the FDA must include in the registry and results database a table of anticipated and unanticipated serious and frequent adverse events. Furthermore, FDAAA requires the FDA to consider the World Health Organization’s consensus data elements for clinical trial results and hold a public meeting to give interested individuals an opportunity to provide input on the regulations.

In addition, Title VIII includes an enforcement mechanism. It requires that all drug, biologic, and device applications or notifications for marketing must include a certification that the manufacturer has satisfied the clinical trial registry and results provisions. A manufacturer who fails to submit the required certification or clinical trial information, or who submits false or misleading clinical trial information, will be subject to a fine of not more than $10,000 for all violations adjudged in a single proceeding, and an additional $10,000 per day fine if the violation is not corrected in 30 days.

Finally, the new law supplants the pre-existing mandatory clinical trial registries established by several of the states. Compliance with the various state programs created issues for manufacturers, and the existence of multiple registries makes it more difficult to search for results. Therefore, FDAAA includes a preemption provision, which states that “no State or political subdivision of a State may establish or continue in effect any requirement for the registration of clinical trials or for the inclusion of information relating to the results of clinical trials in a database.” FDAAA §801(d)(1).

Some manufacturers were concerned that publication of clinical trial results for an as-yet unapproved use might be construed as off-label marketing or promotion. To alleviate that concern, FDAAA explains in a rule of construction that if information is submitted in compliance with the new law, “[t]he fact of submission of clinical trial information… that relates to a use of a drug or device not included in the official labeling of the approved drug or device shall not be construed… in any administrative or judicial proceeding, as evidence of a new intended use of the drug or device that is different from the intended use of the drug or device set forth in the official labeling of the drug or device.”
ability of clinical trial information through the registry and results data bank… shall not be considered as labeling, adulteration, or misbranding of the drug or device under the [FD&C Act]. 16 Id. §801(d)(2).

**Title IX: FDA Authority for the Post-Market Safety of Drugs**

Title IX has been described as “the centerpiece of [FDAAA’s] attempt to enhance post-market drug safety.” House Committee on Energy and Commerce Report 110-225 (July 11, 2007). Most notably, as discussed below, Title IX expressly authorizes the FDA to (1) develop a means to engage in “active surveillance” or pharmacovigilance of post-approval drug safety issues; (2) require an applicant to submit and execute a Risk Management and Mitigation Strategy, or REMS; (3) require post-approval studies and clinical trials; and (4) require post-approval, safety-related label changes. We will address these powers in the order listed above in the following subsections of the article—which is quite different from the order in which they appear in the statute—because we believe the FDA will view them as a spectrum of safety-related tools, ranging from the least intrusive (pharmacovigilance) to the most intrusive (ordering a label change), and that its preference should and will be to consider them in this order.

Title IX also includes provisions allowing the FDA to require pre-submission and review of certain direct to consumer advertising, and other miscellaneous safety-related provisions. These provisions also are discussed below.

**Post-Market Risk Identification and Analysis**

In what may prove to be one of its most groundbreaking and controversial provisions, §905 of FDAAA directs the FDA (in collaboration with the public, academics, and private entities) to develop validated methods to obtain access to, and combine, different data sources for the establishment of an active post-market risk identification and analysis system. Although the science, technology, and statistical validity remain unknown, the goal is to create a system that links and analyzes data from multiple and diverse sources to monitor drug safety. If such a system is created, it is inevitable that the FDA will—at least in part—base its post-market regulatory decisions upon its results, which may profoundly affect product liability litigation.

Within one year after the development of the mandated, necessary risk identification and analysis methods, the FDA must establish and maintain procedures (1) for risk identification and analysis based on electronic health data; (2) for reporting data on all serious adverse drug experiences submitted to the FDA by patients, providers, and drug sponsors; (3) to provide for active adverse event surveillance using various public and private data sources; (4) to identify certain trends and patterns; (5) to provide regular reports concerning adverse events; and (6) to enable the program to export data for further aggregation, statistical analysis, and reporting.

The FDA already has a surveillance system in place in the form of its Adverse Events Reporting System (AERS), and is working to upgrade its AERS database. “What Does AERS Mean? FDA Takes a Close Look at Spontaneous Reporting,” 70 The Pink Sheet No. 6, p. 31 (Feb. 11, 2008). “[A]dverse event reports remain really critical to what we do,” says the FDA’s Office of Surveillance and Epidemiology Director Gerald Dal Pan. Id.

But FDAAA dictates that the future of pharmacovigilance lies in the active review of large databases of patient information from health insurers, HMOs and other sources. Critics of previous surveillance methods note that drug approvals necessarily are based on clinical trial and study data from far fewer patients than will be exposed to the drug post-market. In addition, patients who take a drug post-approval may have different profiles than those who participated in pre-approval clinical trials, and may be exposed to the drug for longer periods. For these and other reasons, safety issues that were not apparent when the drug was approved may reveal themselves over time.

The FDA is anxious to move forward on the surveillance front, according to the FDA’s Dr. Woodcock, but recognizes that it faces significant hurdles. For example, the FDA already has access to a number of databases containing patient information of various kinds, but combining large databases raises serious issues. Because the science is not yet developed, the FDA acknowledges that it does not yet know how (or if) it can validly analyze data from multiple and unhomogeneous databases, but it intends to find out. Dr. Woodcock expects that the FDA will enlist academics and involve the pharmaceutical companies in the project. Indeed, this might be an area where the Reagan-Udall Foundation would become involved.

The devil will be in the details. At most, any such system likely could be used only to detect “signals” of varying degrees of clarity, and to generate hypotheses. The validity and significance of many signals surely will be disputed, not only in the regulatory realm, but in product liability actions as well. In the future, experts in product liability cases will debate the validity and significance of findings based on the FDA’s active surveillance system, just as they now debate the significance of the results of clinical trials and epidemiological studies. Moreover, plaintiffs and their allies will mine the enhanced database, looking for additional targets.

As discussed below, FDAAA implicitly recognizes the limitations of the proposed active surveillance system. It expressly authorizes the FDA to order post-market studies and clinical trials to assess known serious risks, assess signals of serious risk, and to identify unexpected potential serious risks, upon a determination that the mandated, necessary risk identification and analysis methods, the FDA must establish and maintain procedures (1) for risk identification and analysis based on electronic health data; (2) for reporting data on all serious adverse drug experiences submitted to the FDA by patients, providers, and drug sponsors; (3) to provide for active adverse event surveillance using various public and private data sources; (4) to identify certain trends and patterns; (5) to provide regular reports concerning adverse events; and (6) to enable the program to export data for further aggregation, statistical analysis, and reporting.

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require the manufacturer to develop and conform to Risk Evaluation and Mitigation Strategies (REMS). Or, it may require a manufacturer to conduct a post-approval study or clinical trial, in order to “assess a known serious risk related to the use of the drug,” “signals of serious risk,” or to “identify an unexpected serious risk when available data indicates the potential for a serious risk.” FDAAA also makes explicit the FDA’s authority to require labeling changes on the basis of new safety information. “New safety information” includes “information derived from a clinical trial, an adverse event report, a postapproval study…, or peer-reviewed biomedical literature; data derived from the postmarket risk identification and analysis system…; or other scientific data deemed appropriate” by the FDA. This last category includes data about a serious risk associated with use of the drug that the FDA has learned of since the drug was approved or since a prior risk evaluation and mitigation strategy was required or assessed, which may include a new analysis of previously known information. Whether the FDA demands a REMS, a study, or a clinical trial will depend on the nature of the risk associated with the drug and what the FDA believes is required to assess the risk.

REMS
REMS, which the FDA defines as “a strategy to manage a known or potential serious risk associated with a drug or biological product,” is not an entirely new concept, but rather an outgrowth of the FDA’s “Development and Use of Risk Minimization Action Plans” (also referred to as RiskMAP Guidance), which the FDA issued in 2005 pursuant to the former version of PDUFA. See Questions and Answers on the Federal Register Notice on Drugs and Biological Products Deemed to Have Risk Evaluation and Mitigation Strategies, available at [http://www.fda.gov/cder/regulatory/FDAAA/FR_QA.htm](http://www.fda.gov/cder/regulatory/FDAAA/FR_QA.htm).

The RiskMAP Guidance advised pharmaceutical manufacturers on (1) initiating and designing plans called RiskMAPs to minimize identified product risks; (2) selecting and developing tools to minimize those risks; (3) evaluating RiskMAPs and monitoring tools; (4) communicating with the FDA about RiskMAPs; and (5) the recommended components of a RiskMAP submission to the FDA. See Guidance for Industry Development and Use of Risk Minimization Action Plans, available at [http://www.fda.gov/cder/guidance/6358fnl.htm](http://www.fda.gov/cder/guidance/6358fnl.htm#_Toc67721183).

Under FDAAA, the FDA can require a REMS if, on the basis of new safety information, it determines that a REMS “is necessary to ensure that the benefits of the drug outweigh the risks.” FDAAA §901(b). A REMS allows for a measured and tailored response to drug safety issues. For example, if a drug is causing safety issues because it is being abused, REMS can limit the distribution channels or require administration by a hospital. Before imposing a REMS, the FDA must consider several factors, including (1) the estimated size of the population likely to use the drug involved; (2) the seriousness of the disease or condition that is to be treated with the drug; (3) the expected benefit of the drug with respect to such disease or condition; (4) the expected or actual duration of treatment with the drug; (5) the seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug; and (6) whether the drug is a new molecular entity. *Id.* §901(b). For approved drugs, applicants have 120 days after FDA notification to submit a proposed REMS. The FDA may also require the manufacturer to distribute a patient package insert with the drug, communicate with health care providers about risks of the drug, and establish procedures to assure safe use that the provider should implement (such as periodic monitoring or tests).

FDAAA states that a drug will be considered misbranded if the manufacturer fails to comply with a REMS requirement, and establishes civil penalties of $250,000 per violation, not to exceed $1 million. If a violation continues after the FDA provides written notice to the responsible person, a civil monetary penalty of $250,000 for the first 30-day period may be imposed, doubling for each subsequent 30-day period, not to exceed $1 million in a 30-day period, and $10 million for all violations adjudicated in a single proceeding.

The ramifications of the REMS provisions remain to be seen. The FDA has signaled, however, that it will use its power to require a REMS sparingly, and it will request a REMS only to address a safety problem that requires intervention. In late March, the FDA announced that it would require the preparation of a REMS for 25 previously approved drugs. See 73 Federal Register 60, March 27, 2008, available at [http://www.fda.gov/cber/guidance/6358fnl.htm](http://www.fda.gov/cber/guidance/6358fnl.htm#_Toc67721183). As with many of FDAAA’s provisions, the FDA’s enhanced role in monitoring post-market safety and implementing strategies to ameliorate newly discovered risks should bolster manufacturers’ arguments that juries should not be deciding whether the manufacturer has done enough to protect consumers. If a manufacturer is required to implement a REMS and complies with the FDA’s demands, it will be able to argue—based on preemption and/or primary jurisdiction—that it should not be held liable for any injuries based on risks considered by the FDA when formulating the REMS. Conversely, if they can overcome the preemption/primary jurisdiction hurdle, plaintiffs will argue that a failure to follow a REMS should bolster state-law damages claims.

The FDA’s Power to Order Post-Market Studies and Clinical Trials
As mentioned earlier, the FDA’s ability under FDAAA to demand further testing depends on the nature of the risk associated with the drug and what additional testing is needed to assess the risk. Under the new law, the FDA can require a manufacturer to perform a “post-approval study” (which presumably means an epidemiological study or meta-analysis) only if the FDA...
first determines that the then-existing reporting and post-market risk identification analysis system is insufficient to address the pertinent safety concern. FDAAA §901(a). The FDA can require a post-approval clinical trial (which presumably could include trials against either placebo or active comparators) only if it first concludes that a post-approval study would not suffice. For each required study or trial, the FDA must demand a timetable for its completion and periodic reports on its status.

By making the FDA's post-market powers more explicit, FDAAA should help curtail state-law “failure to test” claims by plaintiffs. In most jurisdictions, a prescription drug manufacturer may be found liable for an injury allegedly caused by its drug if the plaintiff shows that the manufacturer failed to provide an adequate warning (rather than, as some jurisdictions hold, when the drug is proven to be “defective.”) This rule derives from comment k to the Restatement of Torts 2d, which acknowledges that products such as prescription drugs “are quite incapable of being made safe for their intended and ordinary use.” As a result, comment k says that “[s]uch a product, properly prepared, and accompanied by proper directions and warning, is not defective, nor is it unreasonably dangerous.” Restatement (Second) of Torts, §402A cmt. k (1965). To prevail, the plaintiff must prove that the drug manufacturer failed to warn of “known or knowable” risks, and that the failure to warn caused the plaintiff's injuries.

Where the risk was not known to the drug manufacturer, plaintiffs have tried to prove that the manufacturer “should have known” of the drug’s risks. In some instances, plaintiffs have argued that the risk was knowable, but was unknown only because the drug manufacturer negligently failed to conduct studies or clinical trials that would have revealed the risk. If the manufacturer had “properly” tested its drug, these plaintiffs argued, it would have discovered additional risk information (or discovered it sooner).

The FDA has long had express authority to require pre-market testing, before the enactment of FDAAA, critics could argue that it lacked explicit authority to require further testing after the drug was already on the market. Although the FDA could request a manufacturer to perform more studies and/or clinical trials (and has always had the authority to withdraw approval for any drug or device it no longer deemed safe and effective under pertinent regulatory standards), most post-approval studies and trials were conducted voluntarily. In response to claims of inadequate pre-market testing, the manufacturer could always defend by pointing out that the FDA had considered the testing adequate and had concluded that the drug was safe and effective (although this did not always allow the manufacturer to escape tort liability). But claims alleging inadequate post-market study or testing were more problematic. Because post-approval testing was usually voluntary, manufacturers could not necessarily argue that their post-market testing (or lack thereof) was sufficient to satisfy FDA requirements.

Courts have struggled with “failure to test” claims for many years. Some early cases entertained inadequate testing as a separate cause of action. See, e.g., Hoffman v. Sterling Drug, Inc., 485 F.2d 132, 142 (3d Cir. 1973) (submitting to the jury the question of whether the defendant had adequately tested its drug over the defendant’s objection that it could not be accused of negligently failing “to conduct animal studies to show the connection between [the drug] and [the alleged harm] at a time when the causal connection was not even suspected in the long term use by humans of the drug”). Ultimately, however, courts in most jurisdictions rejected this theory and held instead that inadequate testing claims are subsumed within causes of action for improper design or failure to warn. Kociemba v. G.D. Searle & Co., 707 F. Supp. 1517, 1527–28 (D. Minn. 1989) (holding that “[i]f the manufacturer designs the product safely, manufactures the product safely, and provides an adequate warning of dangers inherent in the use of the product, then a failure to test the product cannot, standing alone, cause any injury”).

Even courts that have embraced a “duty to test” have never articulated a workable standard specifying when the duty attaches, and what it entails. The questions of when to test, what types of tests can be performed, and how to perform them are complicated. Issues that must be taken into account include: what information is available about adverse events, the number of events, the nature of the risk, and the reliability of that information; what types of studies should be performed, whether the study that should be performed is technologically feasible, whether the study is ethically permitted (doctors and scientists are not allowed to conduct a study on human beings for the sole purpose of determining whether it causes a harm—there must be some potential benefit to the patient); and whether additional warnings or other risk mitigation measures could take the place of further testing. Another concern regarding the pre-approval period is that excessive testing may needlessly delay the availability of important and even lifesaving new medicines. These are issues that courts have not often considered and that are usually beyond the ken of the jury. As a result, an inchoate and contradictory body of law has developed. Courts recognizing a duty to test have proven incapable of giving drug manufacturers sufficient guidance on what, if any, post-market testing should be performed.

FDAAA, however, will now provide that post-marketing testing guidance. Manufacturers must conduct post-market testing when the FDA requires it. (Of course, they remain free to conduct additional testing on a voluntary basis). FDAAA, therefore, strengthens the manufacturers’ position that courts should not permit juries to decide questions of inadequate testing. In addition, because (in most jurisdictions) inadequate testing claims are subsumed by failure to warn claims, all of the arguments in favor of preemption of failure to warn claims apply. This has always been true of claims regarding pre-approval testing, and with FDAAA specifying the FDA's post-approval powers, is now demonstrably true for claims of inadequate post-market testing as well. As a policy matter, the FDA, with its battery of experts and public health perspective that requires the balancing of both risks and benefits, is in a much better position than lay jurors to determine whether additional studies or clinical trials should be undertaken in response to risk information, and/or whether additional warnings or risk mitigation strategies are required.

The FDA’s Power to Order Post-Market Label Changes

FDAAA also provides the FDA with a new
procedure to regulate post-market labeling information. Under the newly created subsection (o)(4) of the existing section 505 of the FDCA (which addresses “New Drugs”), if the FDA becomes aware of new safety information and notifies the manufacturer that it believes the information should be included in a drug’s label, the manufacturer has 30 days to submit a supplement proposing labeling changes or explain why it does not believe that any changes are warranted. FDAAA §901(a).

If the FDA disagrees with the manufacturer, it must initiate discussions with the manufacturer within 30 days. Within 15 days of the conclusion of those discussions, the FDA may issue an order directing the manufacturer to make a labeling change.

These provisions should bolster arguments that state law claims should be preempted in cases where the FDA was aware of new safety data but has chosen not to require a label change. At a minimum, the new procedures should enable defendant manufacturers to argue more forcefully, in cases where the FDA has not exercised its authority to require such a change, that the manufacturer acted reasonably in not initiating one. And of course, the FDA’s express authority to order such changes should provide juries and the public with additional peace of mind that consumers are receiving appropriate drug safety information.

**Preemption and the Rule of Construction**

The ongoing dispute about federal preemption of state-law failure to warn and other claims almost killed FDAAA. In an early draft of the bill, the plaintiffs’ bar lobbied for inclusion of an anti-preemption provision that stated: “Nothing in this act or the amendments made by this act may be construed as having any legal effect on any cause of action for damages under the law of any state (including statutes, regulations, and common law).” Not surprisingly, the pharmaceutical industry strenuously objected. After the industry threatened to withdraw its support for the bill, the provision was removed and replaced with a “rule of construction” that ultimately was enacted as part of part of section 901 of FDAAA: “This paragraph shall not be construed to affect the responsibility of the responsible person or the holder of the approved application under section 505(j) to maintain its label in accordance with existing requirements, including Subpart B of Part 201 and Section 314.70 and 601.12 of Title 21, Code of Federal Regulations (or any successor regulations).” The rule of construction now appears as a new subsection (o)(4)(I) of section 505 of the FDCA.

During the congressional debates, partisans from each side of the preemption dispute expressed conflicting views about whether the FDCA preempts state law claims, and FDAAA’s supposed impact on the issue. For example, Senator Kennedy expressed the opinion that the rule of construction “makes clear” that Congress did not intend to preempt state law regarding the responsibilities of manufacturers to notify consumers of drug risks. See September 20, 2007 Senate Floor Statements, S11834-35. Senator Coburn, on the other hand, opined that the “newly expanded role of the FDA” under FDAAA “does and should preempt state law when it comes to drug safety and labeling.” He went on to embrace the rationale of preemption, explaining that “[n]othing in this rule of construction changes the FDA’s ‘ultimate authority over drug labeling.’” Id. at S11839, S11840.

The rule of construction, however, says nothing either way on the issue of preemption of state law. First, on its face, the rule applies only to “[t]his paragraph.” “This paragraph” seems to refer only to FDCA subsection 505(o)(4) (“Safety Labeling Changes Requested By Secretary.”) Other language in FDAAA Section 901 using the terms “paragraph” and “subparagraph” supports that interpretation. See, e.g., the portion of FDAAA §901(a) creating new FDCA §505(o)(3)(D)(I)–(ii), 505(o)(3)(E)(i)–(ii), 505(o)(3)(F), 505(o)(4)(B), 505(o)(4)(F)–(H), 505-1(a)(2)(A)–(B). Thus, if the rule of construction says anything about preemption, it is limited to the effect on preemption of the new provision expressly authorizing the FDA to order post-market label changes.

Second, and more importantly, by its plain language, the rule says nothing about state law claims. Instead, it speaks only of federal law, and more specifically states that any responsibilities that a manufacturer had under certain federal regulations that were in existence before FDAAA (C.F.R. section 314.70 (“Supplements and other changes to an approved application”) and 601.12 (“Changes to an approved application”) are not affected by the new FDAAA provision on post-market label changes. In short, the rule of construction stands for the unremarkable proposition that the labeling provision of FDAAA does not supplant existing federal labeling regulations.

Although some plaintiffs will likely point to the congressional debates to argue that the rule of construction evinces congressional intent to preserve state law claims, the statements of individual members of Congress should be disregarded. See, e.g., Lamie v. United States Trustee, 540 U.S. 526, 534 (2004) (“when the statute’s language is plain, the sole function of the courts—at least where the disposition required by the text is not absurd—is to enforce it according to its terms.”) The law is well-settled that “the remarks of a single legislator, even the sponsor, are not controlling in analyzing legislative history.” General Dynamics Land Systems, Inc. v. Cline, 540 U.S. 581, 599 (2004). See also Zubor v. Allen, 396 U.S. 168, 186 (1969) (“floor debates reflect at best the understanding of individual Congressmen”). This rule is especially apt in situations like this one, where the statements conflict with each other.

Furthermore, neither the rule of construction nor any other provision of FDAAA purports to alter the preemption preamble to the January 24, 2006, drug labeling rule, in which the FDA proclaimed that its decisions on prescription drug labeling preempt “conflicting or contrary” state law requirements, whether arising by statute, administrative rule, or product liability actions. The Supreme Court will decide the preemption question next term in Wyeth v. Levine. In all likelihood, FDAAA’s “rule of construction” will merit no more than
a footnote in that case, if it is mentioned at all.

Moreover, the express post-market authority included in Title IX of FDAAA can only be read to increase the FDA’s power and reach, and therefore should bolster the case for preemption. Through FDAAA, Congress has in some cases expanded and in others made more explicit the FDA’s post-market duties, rights, and powers. Congress has mandated that the FDA actively review the information that becomes known after the drugs are on the market, and empowered it to take actions such as requiring REMS, post-market studies or clinical trials, and also label changes, as and when the FDA deems such actions appropriate. State laws should not be permitted to intrude on this comprehensive and nuanced regulatory regime by creating their own, often contradictory, standards for testing, marketing, and labeling of FDA-approved drugs.

Prereview of DTC Advertisements
FDAAA gives the FDA authority to require prereview of television advertisements. FDAAA §901(d)(2). The FDA may “recommend” changes to advertisements if necessary to “protect the consumer good and well-being” or to make them consistent with the prescribing information. In addition, if the FDA determines that a television ad otherwise would be false or misleading, it may require specific disclosures, such as a disclosure about a serious risk listed in the drug’s labeling. The new law also requires that any DTC television or radio advertisement present the major statement relating to the drug’s side effects in a clear, conspicuous, and neutral manner. A manufacturer that airs advertisements that are “false or misleading” may be subject to civil penalties: $250,000 for the first violation in a three-year period, with a cap of $50,000 for each subsequent violation in that same period.

For print advertisements, FDAAA requires that all published DTC drug ads include the following statement: “You are encouraged to report negative side effects of prescription drugs to the FDA. Visit http://www.fda.gov/medwatch or call 1-800-FDA-1088.” The FDA is required undertake a study to determine whether the same statement should also be required in television advertisements. FDAAA §906.

Alert defense counsel should use FDAAA’s new DTC provisions to counter plaintiffs’ advertising claims, particularly where the FDA has reviewed the advertisement without objection (or where the objection has been resolved to the FDA’s satisfaction). The Supreme Court is currently deciding whether to grant certiorari on the question of whether the FDCA preempts state law false-advertising claims because the FDA has “exclusive authority” to regulate prescription drug advertising. See Pennsylvan ia Employees Benefit Trust Fund v. Zeneca, Inc., 499 F.3d 239 (3d Cir. 2007) (cert. petition filed December 18, 2007 (No. 07-822)). In addition to preemption, defense counsel may argue that the state court should defer to the primary jurisdiction of the FDA over drug advertising, that FDA-approved ads are not false and misleading as a matter of law, and/or that they fall under “safe harbors” of state law.

Title X: Food Safety
Title X of FDAAA addresses human and pet food safety issues. Among other things, it creates a Reportable Food Registry to facilitate the tracking of, and allow a more rapid response to, foods “for which there is a reasonable probability that the use of, or exposure to… will cause serious adverse health consequences or death to humans or animals.” FDAAA §1005(b). It also requires the FDA to develop a searchable website for posting information about food recalls. Plaintiffs’ lawyers will no doubt monitor both the Registry and the website looking for product liability targets. Title X additionally requires the FDA to establish and/or update standards for pet food ingredients, processing, and labeling.

Title XI: Miscellaneous Provisions
Title XI of FDAAA includes miscellaneous provisions on various topics. One provision that may tangentially affect products liability claims requires the FDA to establish written policies governing the submission and review of articles, books and other published writings by FDA employees. It is not unheard of for FDA employees to take partisan positions, and to play a role in product liability cases.

Conclusion
FDAAA has the potential to transform the FDA’s approach to post-market drug safety, and to affect future products liability claims in areas such as risk identification and assessment, the availability of clinical trial results, FDA-compelled REMS, post-market studies and clinical trials, DTC advertising, and preemption. Future regulations and cases arising from FDAAA should be closely watched, as they may significantly impact product liability litigation.