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FDA Amendments Act of 2007 (P.L. 110-85)

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Summary

On September 27, 2007, the Food and Drug Administration Amendments Act of 2007 (FDAAA; H.R. 3580) was signed into law (P.L. 110-85). The comprehensive law reauthorizes four expiring Food and Drug Administration (FDA) programs and expands the agency's authority to regulate the safety of prescription drugs and biologics, medical devices, and foods.

At its core, FDAAA renews the authority for two key user fee programs that were set to expire on October 1, 2007: the Prescription Drug User Fee Act (PDUFA; P.L. 107-188) and the Medical Device User Fee and Modernization Act (MDUFMA; P.L. 107-250). In FY2007, the year in which FDAAA was enacted, these programs accounted for 91% of FDA's user fee revenue and 18% of FDA's total budget. Without the reauthorizations, and absent a substantial increase in FDA's annual appropriations, the agency would have lost a significant amount of funding.

In addition to user fee programs, FDAAA reauthorizes two other FDA authorities related to prescription drugs for pediatric populations, which were also due to expire on October 1, 2007: the Best Pharmaceuticals for Children Act (BPCA; P.L. 107-109) and the Pediatric Research Equity Act (PREA; P.L. 108-155). These laws provide marketing exclusivity incentives and requirements for studying pediatric use of drugs. FDAAA also contains provisions related to drug safety, pediatric medical devices, clinical trial databases, the creation of a new nonprofit entity to assist FDA with its mission, and food safety.

This report presents a detailed summary of provisions in FDAAA. Each section of the report begins with background information about the FDA relevant to the passage of FDAAA and some references, if appropriate, to the two bills that formed its basis (S. 1082 and H.R. 2900); describes FDAAA's contents; and analyzes how FDAAA changed the law. The report also contains links to pertinent CRS reports. This report, which is intended for reference use, will not be updated other than to reflect any technical changes that Congress might enact.

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Introduction

The Food and Drug Administration Amendments Act (FDAAA; P.L. 110-85) was signed into law on September 27, 2007. The law reauthorizes four expiring Food and Drug Administration (FDA) programs and expands the agency's authority to ensure the safety of prescription drugs and biologics, medical devices, and foods. FDAAA represents the most comprehensive FDA legislation since the Food and Drug Administration Modernization Act of 1997 (FDAMA; P.L. 105-115).

The primary impetus for the legislation was the renewal of FDA's authority for two key user fee programs that were set to expire at the end of FY2007: the Prescription Drug User Fee Act (PDUFA, last reauthorized in 2002; P.L. 107-188), and the Medical Device User Fee and Modernization Act (MDUFMA, enacted in 2002; P.L. 107-250). The law also reauthorizes two other expiring authorities, which are related to pediatric pharmaceuticals: the Best Pharmaceuticals for Children Act (BPCA, last reauthorized in 2002; P.L. 107-109), and the Pediatric Research Equity Act (PREA, enacted in 2002; P.L. 108-155).

In addition to the reauthorizations, FDAAA contains several other FDA-related provisions. These include provisions designed to enhance drug safety, spark the development of pediatric medical devices, expand the types of trials and the substance of information in clinical trial databases, create a new nonprofit entity to assist FDA with its mission, improve food safety, and affect a number of other areas related to public health. Several of FDAAA's provisions contain the authorization to appropriate funding; these are listed in **Appendix A**. Many create additional responsibilities with deadlines for federal agency personnel; see **Appendix B**. In addition, several of the authorities have sunset dates in 2012 or early 2013; see **Appendix C**.

Food and Drug Administration Basics

The FDA, an agency within the Department of Health and Human Services (HHS), regulates the *safety* of most human foods,[1] all animal feeds, and certain other

[1] The United States Department of Agriculture (USDA) regulates the safety of meat and poultry products.

products such as cosmetics.[2] The agency also regulates the *safety and effectiveness* of human drugs, biologics (e.g., vaccines), medical devices, and animal drugs.[3] Those products regulated for effectiveness must be reviewed and approved by FDA before they can be placed in commerce, a process called *premarket approval*. (FDA is tasked with postmarket surveillance for these products as well.) Products regulated only for safety may enter commerce with little FDA oversight, though the agency may inspect production facilities and require that certain good manufacturing practices be carried out. FDA has the statutory authority to withdraw from commerce any product it regulates that it determines to be unsafe.

Media coverage of issues related to the safety of food (e.g., spinach), drugs (e.g., Vioxx), and medical devices (e.g., cardiac stents) has brought congressional attention to FDA's performance and the funding it has available to carry out its statutory responsibilities. For those products requiring premarket approval, a central issue for Congress is how best to balance the need for the agency to help speed the products it regulates to market if they are safe and effective, and correct them, or keep them from entering or staying on the market, if they are not. For human foods, animal feeds, and other products not requiring premarket approval, key issues relate to FDA's ability to assure product safety and protect public health by preventing health threats from occurring, or by identifying and responding to problems quickly.

Legislative Background: S. 1082 and H.R. 2900

Prior to the introduction of H.R. 3580, the bill enacted as FDAAA, each chamber of Congress had passed its own version of comprehensive FDA reauthorization and reform legislation. These were the Food and Drug Administration Revitalization Act (S. 1082), and the Food and Drug Administration Amendments Act of 2007 (H.R. 2900). While most of the bills' provisions were similar, S. 1082 contained some provisions that were not present in H.R. 2900 on the topics of food safety, prescription drug importation, and domestic pet turtle market access. Of those, only the food safety provisions were adopted in FDAAA. See **Table 1** for a listing of major topics covered in each bill.

For background information on the two bills that formed the basis of H.R. 3580, see the archived CRS reports:

- CRS Report RL34089, *FDA Legislation in the 110th Congress: A Guide to S. 1082 and H.R. 2900*, by Erin D. Williams, Susan Thaul, and Donna V. Porter.
- CRS ReportRL34102, *FDA Legislation in the 110th Congress: A Side-by-Side Comparison of S. 1082 and H.R. 2900*, by Erin D. Williams, Susan Thaul, Sarah A. Lister, Donna V. Porter, and C. Stephen Redhead.

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[2] For more information on Public Health Service agencies, see CRS Report RL34098, *Public Health Service (PHS) Agencies: Background and Funding*, by Pamela W. Smith, et al.

[3] The regulation of biologics for animal use is overseen by the USDA.

Table 1. Origins of FDAAA: Topics Addressed in S. 1082, H.R. 2900, and FDAAA

Subject	S. 1082	H.R. 2900	FDAAA
Prescription Drug User Fees	X	X	X
Medical Device User Fees	X	X	X
Medical Device Regulation	X	X	X
Pediatric Exclusivity Incentives (BPCA)	X	X	X
Mandatory Pediatric Assessments (PREA)	X	X	X
Pediatric Medical Devices	X	X	X
Drug Safety	X	X	X
Antibiotic Drugs	X	X	X
Clinical Trials Databases	X	X	X
Conflicts of Interest	X	X	X
Reagan-Udall Foundation	X	X	X
Importation of Prescription Drugs	X	—	—
Food Safety	X	—	X
Domestic Pet Turtle Market Access	X	—	—
Other Provisions	X	—	X

Report Roadmap

The remaining sections of this report contain descriptions of the key FDA programs addressed in FDAAA. FDAAA includes eleven titles, each of which is discussed below in its own section of this report. Each section introduces the topic, surveys the ways in which new provisions changed the law, provides links to relevant CRS reports, and presents a detailed table comparing FDAAA-enacted provisions to any existing previous law. The one exception is Title X, Food Safety, which is described briefly in this report, but addressed in more detail in a separate CRS report.[4] In the text and tables, the Commissioner means the FDA Commissioner, and the Secretary means the HHS Secretary. The report uses several other acronyms as well, all of which are spelled out at their first point of use and in **Appendix D**.

For clarity, the tables comparing FDAAA with previous law have the following attributes. Table provisions are cited to their location in FDAAA. Where applicable, cites are also included for the Federal Food, Drug, and Cosmetic Act (FFDCA), the Public Health Service Act (PHSA), and the United States Code (USC). The USC citations vary in specificity to match the citations listed in FDAAA. When table text

[4] CRS Report RS22779, *Food Safety: Provisions in the Food and Drug Administration Amendments Act of 2007*, by Donna V. Porter.

extends across previous and current law fields, this indicates one of two things. If an FDAAA cite is present, FDAAA is reauthorizing or restating portions of provisions identical to those of the prior law. If no FDAAA cite is present, a preexisting law interacts with and is fundamental to interpreting FDAAA, but has not been amended by it.

Title I. Prescription Drug User Fee Amendments of 2007

Title I of FDAAA, the Prescription Drug User Fee Amendments of 2007 (referred to as PDUFA IV), provides a five-year extension of FDA's authority to collect user fees from manufacturers of drug and biological products and expands the authorized uses of fee revenue.[5] User fee revenue has provided an increasing proportion of FDA funding since PDUFA was first enacted in 1992. In FY1994, the first year FDA noted PDUFA revenue use in its budget justification documents, the fees contributed 9.7% of the human drug program's budget. At the time of FDAAA's passage, the FY2007 budget showed that PDUFA fees made up 44.7% of the agency's human drug program budget.[6]

For further information, see CRS Report RL33914, *The Prescription Drug User Fee Act (PDUFA): Background and Issues for PDUFA IV Reauthorization*, by Susan Thaul.

In the years leading to PDUFA's enactment in 1992, FDA, consumers, and manufacturers all sought to shorten the time between a manufacturer's submission of an application and the agency's decision on whether to approve the product. FDA lacked the funding for staff to review those products quickly. With PDUFA, Congress gave FDA a revenue source to supplement direct appropriations. Congress also structured PDUFA to restrict the use of collected funds to new product review, and established a mechanism for agency-industry collaboration to create performance goals that set targets, primarily for review times.

PDUFA has had a range of effects. New application review times decreased from 29 months in 1987 to 17 months in 1994.[7] PDUFA's restriction of the use of fee revenue to premarket review created what many saw as an imbalance between resources available to premarket and postmarket activities. In its 1997 and 2002

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[5] PDUFA was first enacted in 1992 in P.L. 102-571. It was reauthorized (PDUFA II) in 1997 as Title I of the Food and Drug Administration Modernization Act (FDAMA, P.L. 105-115); and again (PDUFA III) as Title V of the Public Health Security and Bioterrorism Preparedness and Response Act of 2002 (P.L. 107-188).

[6] CRS Report RL34334, *The Food and Drug Administration: Budget and Statutory History, FY1980-FY2007*, by Judith A. Johnson (coordinator), Donna V. Porter, Susan Thaul, and Erin D. Williams.

[7] FDA, *Third Annual Performance Report: Prescription Drug User Fee Act of 1992, Fiscal Year 1995, Report to Congress*, December 1, 1995, at [http://www.fda.gov/ope/pdufa/report95.html].

reauthorizations, Congress gave FDA limited authority to use some of the fees for postmarket safety activities.

During 2004 discussions in preparation for PDUFA IV, several safety problems with aggressively marketed drugs — such as Vioxx — received wide publicity. This heightened the ongoing concern over the balance of attention between premarket review and postapproval safety monitoring. FDAAA reflects that increased focus on postapproval drug safety throughout, but especially in this title, described below, and in Title IX (Enhanced Authorities Regarding Postmarket Safety of Drugs), discussed later in this report.

Title I of FDAAA addresses types of fees, authorized fee revenue, authorized uses of fees, new fees for the advisory review of direct-to-consumer television advertisements, reauthorization and report requirements, and effective dates, as summarized in the following material.

Types of Fees. FDAAA reauthorizes the assessment, collection, and use of three types of fees from manufacturers of drugs and biological products. These are application fees, establishment fees, and product fees.

Authorized Fee Revenue. FDAAA establishes fee revenues, for each fiscal year, of $392,783,000, with various adjustments for inflation, workload, rent and rent-related expenses, and final-year adjustments. Congress added to that base amount fee revenues for drug safety totaling $225 million over the five-year reauthorization.

Authorized Uses of Fees. The new law expands the list of postmarket safety activities for which the fees could be used. These include developing and using adverse-event data-collection systems, including information technology systems; developing and using improved analytical tools to assess potential safety problems, including access to external data bases; and implementing and enforcing new FFDCA requirements relating to postapproval studies and clinical trials, labeling changes, risk evaluation and mitigation strategies, and adverse event reports and postmarket safety activities.

FDAAA also removes the calendar and time limitations on postapproval activities. When Congress first allowed PDUFA revenue use on postmarket activities in 2002, it set a three-year limit from the time of a drug's approval.

New Fees for Advisory Review of Advertisements. FDAAA creates a new user fee to support FDA's advisory review of prescription-drug television advertising. The program calls for a manufacturer to pay a fee if it voluntarily submits an advertisement for pre-dissemination review. The review is to be advisory. The law authorizes FDA to assess fees only on manufacturers that request such reviews. It further directs that if the Secretary has not received at least $11.25 million in fees by 120 days after enactment, the DTC advisory review user fee program shall not commence and all collected fees shall be refunded.

Reauthorization and Report Requirements. FDAAA codifies certain core elements of the prescription drug user fee program that, although included in PDUFA I, II, and III, were never placed into the FFDCA. One is the requirement for annual

performance and fiscal reports to Congress. The others relate to the Secretary's interaction and communication with various stakeholders. These include public hearings regarding the Secretary's negotiations with industry regarding performance goals; and the requirement that the Secretary, in preparation for the next PDUFA reauthorization, consult with congressional committees, scientific and academic experts, health-care professionals, representatives of patient and consumer advocacy groups, and the regulated industry to develop recommendations for PDUFA V, including goals and plans for meeting the goals.

Effective Dates. The amendments in this title took effect on October 1, 2007. Authority to assess, collect, and use drug fees ceases to be effective October 1, 2012. The reporting requirements cease to be effective January 31, 2013.

Table 2. Comparison of *Prescription Drug User Fee Amendments of 2007 (FDAAA Title I)* with Previous Law

Topic	Previous Law	FDAAA Title I
Types of Fees	There are three types of fees — application, establishment, and product — and certain exceptions. [FFDCA 736(a); 21 USC 379h]	
Application Fee	A human drug *application* fee is assessed for an application for which clinical data with respect to safety or effectiveness are required for approval. An application that does not require clinical data or for a supplement is assessed half the application fee. The fee is due at the time of application or supplement submission. Exceptions are made for a previously filed application or supplement under certain conditions and for a designated orphan drug or indication. There is a 75% fee refund if an application is refused for filing. [FFDCA 736(a)(1); 21 USC 379h]	
		The refund provision includes an application withdrawn without a waiver before filing. [FDAAA 103(a)(2); FFDCA 736(a)(1)(D); 21 USC 379h(a)] An application or supplement that is resubmitted following an earlier refusal or withdrawal is required to pay the full fee, unless the fee otherwise is waived or reduced. [FDAAA 103(a)(2); FFDCA 736(a)(1)(E); 21 USC 379h(a)]
Establishment Fee	A prescription drug *establishment* fee is assessed annually for each establishment listed as manufacturing the prescription drug product named in an approved human drug application. [FFDCA 736(a)(2); 21 USC 379h]	
		The annual establishment fee regarding an approved human drug application for a compounded positron emission tomography (PET) drug is one-sixth the annual establishment fee. A not-for-profit medical center that produces PET drugs and uses at least 95% of them within the facility is excepted from the drug establishment fee. [FDAAA 103(a)(3); FFDCA 736(a)(2)(C); 21 USC 379h(a)] Certain applications for orphan drugs are exempted from facility fees. [FDAAA 103(f); FFDCA 736(k); 21 USC 379h]
Product Fee	A prescription drug *product* fee is assessed annually for each prescription drug product named in an application (except for a product whose manufacturer has had no pending application since September 1992). [FFDCA 736(a)(3); 21 USC 379h]	
		Certain applications for orphan drugs are exempt from product fees. [FDAAA 103(f); FFDCA 736(k); 21 USC 379h]

Topic	Previous Law	FDAAA Title I
Authorized Uses of Fees	The law authorizes FDA to use the fees for "the review of human drug applications." It defines the term "process for the review of human drug applications" as: activities necessary for the review of human drug applications and supplements; the issuance of action letters; inspection of prescription drug establishments and other facilities; activities necessary for the review of applications for licensure of biological product establishments and for the release of lots of biologics; and monitoring of research conducted in connection with the review of human drug applications. [FFDCA 735(6); 21 USC 379g]	
	For drugs approved after Oct. 1, 2002, the collecting, developing, and reviewing of safety information on the drugs, including adverse event reports, during a period of time after approval of such applications or supplements, not to exceed three years.	The list of postmarket safety activities for which the fees could be used also includes: adverse event data collection systems and improved analytical tools, increased requirements for adverse event reporting both to the Secretary and to the public, and enforcement of study and label-change requirements. There are no longer calendar and time limitations on postapproval activities. [FDAAA 102; FFDCA 735(6)(F); 21 USC 379g]
	The term "costs of resources allocated for the process for the review of human drug applications" is defined as expenses and costs for: FDA officers, employees, contractors, and advisory committees; information management; computer resources; facilities, furniture, equipment, materials and supplies; and collecting user fees and accounting for resources. [FFDCA 735(7); 21 USC 379g]	
Fee Revenue Amounts	The law established revenue amounts, subject to specified adjustments, that each type of fee would generate for each of FY2003 through FY2007. For FY2007, the total fee revenue authorized was $259,300,000, evenly divided among Application, Establishment, and Product fees, as required.	FDAAA establishes total prescription drug user fee revenues, for each fiscal year, of $392,783,000, with various adjustments. It requires that each fee type provide one-third of the total revenue. [FDAAA 103(b); FFDCA 736(b)(1,2); 21 USC 379h(b)]
Additional Fee Revenues for Drug Safety	No provision.	The law directs that, in addition to the adjusted revenue value based on $392,783,000, there be fee revenues collected and used for drug safety in specific amounts summing to $225 million from FY2008 through FY2012. [FDAAA 103(b); FFDCA 736(b)(4); 21 USC 379h(b)]
Inflation Adjustment	The inflation adjustment was based on the Consumer Price Index (all U.S. urban) for the previous year or the total percent change in the previous year in General Schedule basic pay, as adjusted by DC-area locality pay. The adjustment was to be compounded to the sum of all adjustments made each fiscal year.	The adjustment for inflation method includes the average annual cost per FDA employee of all personnel compensation and benefits. [FDAAA 103(c)(1); FFDCA 736(c)(1); 21 USC 379h(b) and 379h(c)]

Topic	Previous Law	FDAAA Title I
Workload Adjustment	Fee revenues are adjusted to reflect changes in FDA's workload for the process for the review of human drug applications. [FFDCA 736(c)(2); 21 USC 379h]	
	The calculation was based on a weighted average of the change in the total number of human drug applications, commercial investigational new drug (IND) applications, efficacy supplements, and manufacturing supplements submitted.	The calculation now counts commercial IND applications as the number that were active during the preceding year. [FDAAA 103(b); FFDCA 736(b)(3); 21 USC 379h(b)]
	The workload adjustment was prohibited to result in fee revenues for a fiscal year that were less than those established as the total fee revenue for that fiscal year, adjusted for inflation.	The number of human drug applications is adjusted for changes in review activities. The adjustment for changes in review activities may not result in more than an additional 2% increase. [FDAAA 103(c)(2); FFDCA 736(c)(2); 21 USC 379h(c)]
	No provision.	The Secretary must contract with an independent accounting firm to study the adjustment for changes in review activities and make any warranted recommendations. The Secretary may not make changes unless the study has been completed, and, once the study has been completed, must make any appropriate changes. [FDAAA 103(c)(2); FFDCA 736(c)(2)(C); 21 USC 379h(c)]
Rent and Rent-Related Cost Adjustment	No provision.	The law directs the Secretary to decrease (up to $11.7 million) the fee revenue total if actual costs paid for rent and rent-related expenses are less than estimates made for such year in FY2006. [FDAAA 103(c)(3); FFDCA 736(c)(3); 21 USC 379h(c)]
Final Year Adjustment	The Secretary may *increase* total fee revenue if necessary to provide for up to three months of operating reserves for the process of human drug application review for the first three months following sunset. [FDAAA 103(c)(4); FFDCA was 736(c)(3), now 736(c)(4)(A); 21 USC 379h(c)]	
	No provision.	The final year adjustment may *decrease* fee revenue if FY2009 or FY2010 appropriations for both FDA and the review of human drug applications exceed the amounts appropriated for those activities for FY2008 — a "reverse trigger." This decrease is limited to a maximum of $65 million. [FDAAA 103(c)(4); FFDCA 736(c)(4)(B); 21 USC 379h(c)]

Topic	Previous Law	FDAAA Title I
Fee Waiver or Reduction	The Secretary must grant a waiver or reduction of fees if necessary to protect the public health, if the fee would be a significant barrier to innovation, if the fee would exceed the cost of the process of review, or if the applicant is a small business that is submitting its first human drug application. [FDAAA 103(d); FFDCA 736(d); 21 USC 379h]	
		FDAAA specifies that the Secretary grants a waiver or reduction of fees to a person who is named as the applicant, and that, in deciding whether to grant a waiver or reduction, the Secretary may consider only the circumstances and assets of the applicant and any affiliate of the applicant. [FDAAA 103(d)(3); FFDCA 736(d)(2); 21 USC 379h]
	A small business is an entity with fewer than 500 employees, including employees of affiliates. [FDAAA 103(d); FFDCA 736(d); 21 USC 379h]	
		Regarding waivers and reductions of fees, the definition of a small business is expanded to narrow eligible businesses to those that do not have a drug product that has been approved under a human drug application and introduced or delivered for introduction into interstate commerce. [FDAAA 103(d); FFDCA 736(d); 21 USC 379h]
Crediting and Availability of Fees	There were authorized to be appropriated prescription drug user fees of $222,900,000 for FY2003; $231,000,000 for FY2004; $252,000,000 for FY2005; $259,300,000 for FY2006; and $259,300,000 for FY2007, as adjusted.	There are authorized to be appropriated, for each of FY2008 through FY2012, prescription drug user fees in the amount determined in FDAAA 103(b), as adjusted.
	The amount of fees collected in excess of the amount specified in appropriations acts is to be (1) credited to FDA's appropriation account, and (2) subtracted from the amount that would otherwise have been authorized to be collected during subsequent fiscal years. [FDAAA 103(e); FFDCA 736(g)(4); 21 USC 379h]	

Topic	Previous Law	FDAAA Title I
	The calculation of excess collections was done for each fiscal year and the offset reflected in the subsequent fiscal year's authorization.	The amount of excess collections is based on a cumulative calculation of fees collected in FY2008, FY2009, and FY2010 and those estimated to be collected in FY2011. The offset must be reflected in the amount authorized to be collected in FY2012. [FDAAA 103(e); FFDCA 736(g)(4); 21 USC 379h]
User Fees for the Advisory Review of Advertisements	No provision.	The law authorizes the assessment and collection of fees relating to advisory review of certain drug advertisements. Manufacturer requests for pre-dissemination review of direct-to-consumer (DTC) television drug advertisements would be voluntary, and FDA responses would be advisory. Only manufacturers that request such reviews would be assessed the new fees, which would include an advisory review fee and an operating reserve fee. The law authorizes $6.25 million in revenue for each of FY2008 through FY2012, adjusted for inflation and workload, and requires the Secretary to establish an operating fund. If, by the later of November 1, 2007, or 120 days after enactment, the Secretary has not received at least $11.25 million in advisory review fees and operating reserve fees combined, the DTC television advertisement advisory review user fee program shall not commence and all collected fees shall be refunded. [FDAAA 104; FFDCA 736A; 21 USC 379h-1]

Topic	Previous Law	FDAAA Title I
Reauthorization	The Secretary is required to submit to congressional committees letters that propose performance goals and user fee amounts for the next round of PDUFA reauthorization legislation. Previous PDUFA legislation required the letters but did not direct that the provision become part of USC Title 21. FDAAA codified this provision. [FDAAA 105; FFDCA 736B(a),(b); 21 USC 379h-2]	
	The proposals result from negotiations, required by FFDCA, between the agency and the pharmaceutical industry.	The Secretary must, in preparation for the next PDUFA reauthorization, consult with congressional committees, scientific and academic experts, health-care professionals, representatives of patient and consumer advocacy groups, and the regulated industry to develop recommendations for PDUFA V, including goals and plans for meeting the goals. A public hearing and review of the Secretary's recommendations must be held following its negotiations with the industry, and the Secretary must include with the submission to Congress a summary of the public comments and changes made to the recommendations in response to them. Before presenting recommendations to Congress, the Secretary must make publicly available on the FDA website the minutes of all agency negotiation meetings with the regulated industry, including summaries of any substantive proposals made by any negotiating party and any significant controversies or differences of opinions and their resolution. [FDAAA 104; FFDCA 736B(d); 21 USC 379h-1]
Annual Reports	The Secretary must submit annual fiscal and performance reports to Congress. Previous PDUFA legislation required the reports but did not direct that the provision become part of USC Title 21. FDAAA codified this provision. [FDAAA 105; FFDCA 736B(a),(b); 21 USC 379h-2]	
	No provision.	The Secretary must make publicly available on the FDA website the annual performance and fiscal reports to congressional committees. [FDAAA 105; FFDCA 736B(c); 21 USC 379h-2]
Sunset Dates	The authority to assess, collect, and use drug fees ceased to be effective October 1, 2007, and the reporting requirements ceased to be effective 120 days later [January 29, 2008].	The authority to assess, collect, and use drug fees ceases to be effective October 1, 2012. [FDAAA 106; not in FFDCA; 21 USC 379g note] The reporting requirements cease to be effective January 31, 2013. [FDAAA 106; not in FFDCA; 21 USC 379h-2]
Effective Date	The provisions took effect on October 1, 2002.	The provisions took effect on October 1, 2007. [FDAAA 107; not in FFDCA; 21 USC 379g note]

Title II. Medical Device User Fee Amendments of 2007

Title II of FDAAA, the Medical Device User Fee Amendments of 2007 (MDUFA 2007), reauthorizes FDA's authority to collect user fees from medical device manufacturers, and makes certain other amendments to the regulation of devices. Congress initially gave the agency the authority to collect such fees in 2002, with the Medical Device User Fee and Modernization Act (MDUFMA; P.L. 107-250). MDUFMA established user fees for premarket applications (PMAs),[8] premarket notifications (510(k)s),[9] and other types of requests to market medical devices. The 2002 law incorporated, by reference, performance goals for many types of premarket device reviews. It also enabled third-parties to conduct establishment inspections, and added new regulatory requirements for reprocessed single-use devices.

For further information, see CRS Report RL33981, *Medical Device User Fee and Modernization Act (MDUFMA) Reauthorization*, by Erin D. Williams.

In FY2007, when FDAAA was enacted, medical device user fees generated $35,202,000. This represents an increase of 144.7% over the amount first collected in FY2003. In FY2007, devices user fees comprised 9.0% of the agency's user fee revenue, and 1.8% of its total budget.[10]

FDA's authority to collect medical device user fees was due to expire on October 1, 2007. Congress reauthorizes the authority in MDUFA 2007, Subtitle A. In Subtitle B, it amends some aspects of the regulation of medical devices. The details of each of these are discussed below.

Subtitle A. Fees Related to Medical Devices

Subtitle A of MDUFA 2007 reauthorizes FDA's expiring authority to collect user fees through October 1, 2012, and makes certain other changes to MDUFMA. The primary change is that MDUFA 2007 adds three new types of user fees (annual establishment fees, registration fees, and 30-day fees). The first two are to be paid regularly by establishments with devices on the market, generating a predictable base of device user fee income for FDA. MDUFMA had only enabled the collection of fees for applications related to FDA's approval or clearance of a product, which the agency had noted made the agency's user fee income difficult to predict. This was because the number of applications could vary from year to year. The agency asserted that, by contrast, fees paid annually would result in a revenue stream that

[8] A PMA is generally required for new medical devices, and those that necessitate FDA's highest level of safety controls.

[9] A 510(k) is generally required for medical devices similar to ones already on the market.

[10] CRS Report RL34334, *The Food and Drug Administration: Budget and Statutory History, FY1980-FY2007*, by Judith A. Johnson (coordinator), Donna V. Porter, Susan Thaul, and Erin D. Williams.

was more reliable. This move toward a more predictable funding stream mirrors the approach taken by PDUFA for drugs and biological products.

MDUFA 2007 lowers the amounts of fees paid by device manufacturers for FY2008, and then includes a subsequent annual increase in fee amounts through FY2012. Despite the FY2008 decrease in the amounts of individual fee amounts, the total fee revenue generated will increase from FY2007 levels; revenue lost in reduced fee amounts will be offset by revenue generated by new types of fees.

MDUFA 2007 changes some provisions relevant to specific types of fees. Both MDUFMA and MDUFA 2007 generally establish fee amounts for various types of activities by setting them as a proportion of the cost of submitting a PMA. The amount charged for a PMA is therefore also called the *base fee*. MDUFA 2007 strikes a provision that had required the Secretary to adjust the premarket notification fee amount annually in a unique way, instead it sets it, like other fees, as a percentage of the base fee amount. For a different fee, the FDAAA-created establishment fee, the law gives the Secretary the authority to increase the fee amount in FY2010 if too few manufacturers have paid it.

MDUFA 2007 changes the law regarding reduced fees paid by small businesses in several ways. Under MDUFMA, entities qualifying as small businesses had certain fees waived and paid others at a reduced rate. MDUFA 2007 further reduces the fee amounts small businesses pay, removes a provision that the assets of partners and parent firms be considered in small business qualification, and enables foreign firms to qualify as small businesses.

Regarding modular applications, those submitted to FDA in separate pieces, MDUFA 2007 for the first time also affords the possibility of refunds for applications withdrawn at different points.

MDUFA 2007 extends a *trigger* requirement beyond FY2007 indefinitely.[11] The trigger, which is designed to ensure that user fees supplement rather than supplant direct appropriations, requires that there be a certain amount of medical device-related direct appropriations in order for the Secretary to assess medical device user fees and be expected to meet performance goals.

MDUFA 2007 amends a provision regarding the collection of fees in excess of the amount authorized. The previous law required that if fees collected for a fiscal year exceed the authorized appropriation, the excess would be subtracted from the subsequent year's authorization. By contrast, MDUFA 2007 allows excess fees to be carried over to cover shortfalls over the course of several years.

MDUFA 2007 amends a provision describing how FDA may use the device fees it collects. The new provision in theory could have enabled fees to be expended on postmarket activites, but does not appear, in practice, to have done so. It states that fees will be dedicated toward expediting the process for the review of device

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[11] The FY2007 trigger was articulated in the Medical Device User Fee Stabilization Act of 2005 (P.L. 109-43).

applications and for assuring the safety and effectiveness of devices, as set forth in a letter from the Secretary to relevant congressional committees ("Commitment Letter").[12] It is conceivable that assuring the safety and effectiveness of devices could be interpreted to encompass postmarket surveillance, however the Commitment Letter does not list surveillance and enforcement activities. In addition, MDUFA 2007 maintains two separate MDUFMA provisions that articulate and generally limit the expenditure of user fee funds to premarket activities.[13]

MDUFA 2007 requires the Secretary to continue to file annual performance and fiscal reports through FY2012, and writes these report requirements into the FFDCA. The law also requires that the performance report include information on previous cohorts for which the Secretary had not given a complete response.

In FDA's development of its performance goal recommendations to the Congress, MDUFA 2007 maintains MDUFMA's requirements that the agency consult with an array of groups, and take specified steps to invite public input. Unlike the previous law, MDUFA 2007 specifies that the recommendations be revised upon consideration of public comments, requires the recommendations' transmittal to Congress, and writes the performance goal-related requirements into the FFDCA.

Separate from the user fee authorizations, MDUFA 2007 authorizes the appropriation of specific sums from FY2008 through FY2012 for the review of postmarket safety information on medical devices. MDUFMA made similar authorizations, though no funds were appropriated.

MDUFA 2007 became effective on October 1, 2007.

Subtitle B. Amendments Regarding Regulation of Medical Devices

Subtitle B of MDUFA 2007 makes various changes to the regulation of medical devices. It extends from FY2007 through FY2012 the authority to have third parties review premarket notifications.

Producers of devices that are marketed in the United States are required to register annually with FDA. MDUFA 2007 restricts the period within which device producers must register with the Secretary. It also reduces from twice to once per year the requirement that those who register with the Secretary provide a list of devices on which they perform specific functions (e.g., the manufacture, preparation, propagation, compounding or processing of a device).

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[12] "Commitment Letter" from Michael O. Leavitt to Edward M. Kennedy, September 27, 2007, at [http://www.fda.gov/cdrh/mdufma/commitmentletter.pdf].

[13] 21 USC 379j(h)(2)(A)(ii), 379i(5). The one partial exception to the premarket general rule was the ability to expend user fee funds on the evaluation of postmarket studies that are required as a condition of approval.

MDUFA 2007 amends electronic registration regulations to require electronic filing as a default, and without necessitating rulemaking by the Secretary as would have previously been required.

MDUFA 2007 amends two portions of the FFDCA's provisions regarding *records and reports on devices*. First, it adds a requirement that the Secretary promulgate regulations establishing a unique identification system for medical devices. Second, it modifies the reporting requirements for devices linked to serious injuries or deaths.

MDUFA 2007 revises the requirements for inspections by accredited third parties in three ways. First, it reduces administrative requirements associated with qualifying for the program. Second, it expands participation in the program. Third, it permits device companies to voluntarily submit to FDA reports by third parties assessing conformance with appropriate international quality systems standards, such as those set by the International Standards Organization. FDA is to consider the information in these reports in setting its inspection priorities.

MDUFA 2007 requires the Comptroller General to conduct two studies, and the FDA to conduct one. The Comptroller General is required to conduct one study on the appropriate use of the process under FFDCA 510(k) (premarket notification) to determine whether a device is safe and effective. It is required to conduct a second study on nosocomial (hospital-acquired) infections associated with medical devices. The FDA is required to conduct a study on whether the relationship between indoor tanning device use and the development of skin damage warrants a label change for the devices.

Table 3. Comparison of *Medical Device User Fee Act 2007, Subtitle A (FDAAA Title II, Subtitle A)* with Previous Law

Topic	Previous Law	FDAAA Title II, Subtitle A
Use of Fees	Fees may be used only for purposes specified in FFDCA 737(8) (formerly 737(5)). (None is related to postmarket inspection and enforcement, except evaluation of postmarket studies required as a condition of approval.)	
	The fees authorized by this title will be dedicated to meeting the goals identified in the Commitment Letter. [MDUFMA 101].	Fees are dedicated toward expediting the review of applications and for assuring the safety and effectiveness of devices, as set forth in the Commitment Letter goals. [FDAAA 201(c); 21 USC 379i note]
	[Commitment letter goals do not include postmarket inspection and enforcement.]	
Types of Fees	All fee types were linked to device-related applications for FDA review. Fees included those for: premarket application (such as a PMA); panel-track PMA supplement; BLA efficacy supplement; 180-day PMA supplement; real-time PMA supplement; 510(k) premarket notification.	Previous fee types are maintained, and three are added. Two are for regularly occurring events: establishment registration and annual filing fees; one is for an application: 30-day notice fee. [FDAAA 211(3); FFDCA 737(5)-(7),(11),(13); 21 USC 379i]
Fee Amounts	Base fee was $281,600 for FY2007. Premarket notification fee was set annually, based on predicted aggregate income generated from all premarket notification fees collected.	Base fee is reduced to $185,000 for FY2008, and it is to increase 8.5% per year. Premarket notification fees are set like all other fees, as a percentage of the base fee. [FDAAA 212(a)(2),(b); FFDCA 738(a)(2)(A), (b); 21 USC 379j(a)(2)(A), (b)]
Payment	Fee payment is due upon submission of application or of request for classification. [FDAAA 212(a)(3); FFDCA 373(a)(2)(C); 21 USC 379j(a)(2)(C)]	
		Requirement is expanded to include new fee types. [FDAAA 212(a)(3); FFDCA 373(a)(2)(C); 21 USC 379j(a)(2)(C)]
Refunds for Modular Applications	No provision.	A 75% refund is specified for modular applications withdrawn before a second portion is submitted and before first action. Applications withdrawn later may be refunded at the Secretary's discretion. [FDAAA 212(a)(4); FFDCA 738(a)(2)(D)(iv)-(vi); 21 USC 379j(a)(2)(D)]

Topic	Previous Law	FDAAA Title II, Subtitle A
Annual Establishment Registration Fee	No such fee.	Secretary may increase the establishment registration fee amount in FY2010 up to an additional 8.5% over the annual 8.5% increase if fewer than 12,250 establishments paid the fee in FY2009. [FDAAA 212(c)(2); FFDCA 738(c); 21 USC 379j(c)] State and federal governmental entities and Indian tribes are exempt from annual establishment fees. [FDAAA 212(a)(5); FFDCA 738(a)(3); 21 USC 379j(a)]
Fees for Small Businesses	In the small business qualification, the assets of partners and parent firms were considered. Qualification requirements depended on an IRS tax filing. Small businesses paid at a rate of 38% of most user fees, and 80% of the premarket notification fee.	In the small business qualification, the assets of partners and parent firms are no longer considered. Qualification requirements may be satisfied by an alternative to an IRS tax filing, so foreign businesses may qualify. Small businesses pay at a rate of 25% of most user fees, and 50% of premarket notification fees. [FDAAA 212(d),(e); FFDCA 378(d),(e); 21 USC 379j(d),(e)]
Effect of Failure to Pay Fees	Applications and requests for classification for which fees apply will not be accepted if fees are not paid. [FDAAA 212(f); FFDCA 738(f); 21 USC 379j(f)]	
		Requirement is expanded to apply to new fee types. [FDAAA 212(f); FFDCA 738(f); 21 USC 379j(f)]
Conditions (Trigger)	Direct appropriations must be more than one percent less than $205,720 multiplied by an adjustment factor, or else the Secretary may not collect user fees and is not required to meet performance goals. [FDAAA 212(g); FFDCA 738(g); 21 USC 379j(g)]	
	Trigger specified through FY2007.	Trigger extended indefinitely. [FDAAA 212(g); FFDCA 738(g); 21 USC 379j(g)]
Authorization of Appropriations	The following amounts of user fees were authorized to be appropriated: $25,125,000 for FY2003; $27,255,000 for FY2004; $29,785,000 for FY2005; $32,615,000 for FY2006; and $35,000,000 for FY2007.	The following amounts of user fees are authorized to be appropriated: $48,431,000 for FY2008; $52,547,000 for FY2009; $57,014,000 for FY2010; $61,860,000 for FY2011; and $67,118,000 for FY2012. [FDAAA 212(h)(1); FFDCA 738(h)(3); 21 USC 379j(h)(3)]
Offset	User fees collected that exceeded the authorized appropriation for a fiscal year must have been subtracted from fees authorized to be collected for the subsequent year.	User fees collected between FY2008 and FY2011 are to be considered in aggregate. A reduction is to be made in fees in the final year (i.e., FY2012) only if the amount collected in the four-year period exceeded the amount authorized for the same period. [FDAAA 212(h)(2); FFDCA 738(h)(4); 21 USC 379j(h)(3)]

Topic	Previous Law	FDAAA Title II, Subtitle A
Reporting Requirements	Secretary is required to submit annually to relevant congressional committees a performance goal report and fiscal report. [MDUFMA 103; and FDAAA 213; FFDCA 738A; 21 USC 379j-1]	
		The requirement is written into the FFDCA. The performance report is to include information on all previous cohorts for which the Secretary has not given a complete response. [FDAAA 213; FFDCA 738A; 21 USC 379j-1]
Performance Goal Development	FDA is required to consult with an array of governmental, professional and consumer groups, publish its recommendations in the Federal Register, provide a public comment period, and hold a public meeting. [MDUFMA 105; and FDAAA 213; FFDCA 738A; 21 USC 379j-1]	
		Recommendations are to be revised upon consideration of public comments, recommendations are to be transmitted to Congress, and performance goal-related requirements are written into the FFDCA. [FDAAA 213; FFDCA 738A; 21 USC 379j-1]
Postmarket Appropriations Authorization	The following amounts were authorized for postmarket surveillance of medical devices (amounts are increases above the FY2002 appropriation): an increase of $3,000,000 for FY2003, an increase of $6,000,000 for FY2004, an increase of such sums as may be necessary for FY2005 and each subsequent fiscal year.	The following amounts are authorized to be appropriated for postmarket safety information on medical devices: $7,100,000 for FY2008, $7,455,000 for FY2009, $7,827,750 for FY2010, $8,219,138 for FY2011, and $8,630,094 for FY2012. [FDAAA 215]
Effective Date	October 1, 2002.	October 1, 2007; savings clause included. [FDAAA 214, 216; 21 USC 379i note]
Sunset	October 1, 2007.	October 1, 2012; for specified reports, January 31, 2013. [FDAAA 217; 21 USC 379i note]

Table 4. Comparison of *Medical Device User Fee Act 2007, Subtitle B (FDAAA Title II, Subtitle B)* with Previous Law

Topic	Previous Law	Title II, Subtitle B
Authority for Review of Third Party Premarket Notification	Authority was set to expire on October 1, 2007.	Authority is set to expire on October 1, 2012. [FDAAA 221; FFDCA 523(c); 21 USC 360mm(c)]
Registration	Medical device producers were required to register with the Secretary prior to December 31 of each year. Device producers that registered with the Secretary were required to provide a list of devices on which they performed specific functions twice per year, in June and December.	Medical device producers must register with the Secretary between October 1 and December 31 of each year. [FDAAA 222; FFDCA 510(b); 21 USC 360(b)] Device producers that register with the Secretary must provide a list of devices on which they perform specific functions once per year (between October 1 and December 31). [FDAAA 223; FFDCA 510(j); 21 USC 360(j)(2)]
Electronic Registration and Listing	Registrants would have had to file by electronic means upon a finding by the Secretary that the electronic receipt was feasible, unless the Secretary granted a request for waiver.	Registrants must file electronically unless the Secretary grants a waiver. [FDAAA 224; FFDCA 510(p); 21 USC 360(p)]
Unique Device Identification System	No provision.	The Secretary is required to promulgate regulations establishing a unique identification system for medical devices. [FDAAA 226; FFDCA 519(f); 21 USC 360i]
Frequency of Reporting for Certain Devices	Device manufacturers and importers were generally required to report serious injuries or deaths associated with their medical devices (adverse event reports).	Adverse event reports must generally comply with 21 CFR 803 (regarding adverse event reporting for medical devices), unless the Secretary grants an exemption or variance. Adverse event reports for devices granted exemptions or variances, as well as for imported devices, are to submitted according to criteria established by the Secretary. [FDAAA 227; FFDCA 519(a)(1); 21 USC 360(i)(a)(1)]

Topic	Previous Law	Title II, Subtitle B
Inspections by Accredited Persons	Program start-up language was included. A maximum of 15 parties could have been accredited. Certain time restrictions applied to device establishment eligibility. One component of eligibility could have been met by submitting a statement that the law of a country in which the device is marketed recognizes an inspection of the establishment by the Secretary. No time period was specified for an establishment or accredited person to respond to a Secretary's request for information. An establishment's use of an accredited party inspection was restricted after a finding of "official action indicated."	Program start-up language is deleted. Accredited party limit is deleted. An accredited person is required to notify the Secretary of any withdrawal, suspension, restriction, or expiration of his or her certificate of conformance. Device establishment eligibility time restrictions are removed. A statement that the law of a country in which the device is marketed recognizes an inspection of the establishment by the Secretary is no longer a component of an establishment's eligibility. An establishment or accredited person is required to respond to a Secretary's request for information within 60 days. The Secretary may deny clearance if information provided is untrue. The "official action indicated" restriction on accredited party inspection is deleted. The Secretary is to take harmonization with international standards into account when specifying the required format for third party inspection reports. [FDAAA 228; FFDCA 704(g); 21 USC 374(g)]
Reports	The Secretary was required to request an IOM study on whether the medical device postmarket surveillance system provided adequate safeguards for pediatric populations.	The Comptroller General is required to conduct one study on the appropriate use of the process under FFDCA 510(k) (premarket notification) to determine whether a device is safe and effective. [FDAAA 225] Another required GAO study concerns nosocomial infections relating to medical devices. [FDAAA 229] The FDA is required to conduct a study on whether the relationship between indoor tanning device use and the development of skin damage warrants a label change. [FDAAA 230]

Title III. Pediatric Medical Device Safety and Improvement Act of 2007

Title III of FDAAA is the Pediatric Medical Device Safety and Improvement Act of 2007 (PMDSIA). PMDSIA was enacted based upon reports of a critical need for pediatric medical devices that help diagnose and treat diseases and conditions affecting children. Apparently, developing medical devices for children is less profitable and more problematic than developing them for adults. Fewer children need medical devices than adults, and children have physical attributes (e.g., size, biochemistry, growth rates), activities, and environmental influences that are different from those of adults.

For further information about medical device approval, see CRS Report RL32826, *The Medical Device Approval Process and Related Legislative Issues*, by Erin D. Williams.

In order to encourage the development of the pediatric devices, PMDSIA creates some new reporting requirements related to certain pediatric devices, offers several types of incentives to manufacturers to create pediatric medical devices, and gives FDA the authority to require postmarket studies of approved pediatric devices to ensure their continued efficacy and safety.

PMDSIA creates a set of reporting requirements for applications made under FFDCA 515 and 520(m).[14] Section 515 governs PMAs to market class III devices (these require FDA's highest level of safety controls). Section 520(m) governs *humanitarian device exemptions* (HDEs). An HDE allows a manufacturer with a device aimed at a U.S. patient population of less than 4,000 to market the product without having to demonstrate its effectiveness (only its safety), and to have certain application fees waived. The exemption from proving effectiveness is designed to encourage manufacturers to develop medical devices for these small markets, assisting patients with rare diseases and conditions who might otherwise not be served. PMDSIA creates requirements for both types of applications, inserting a new section, 515A, into the medical device approval regulations.

Section 515A requires those requesting approval to market a device under 515 and 520(m) to include, if readily available, a description of any pediatric subpopulation with the disease or condition that the devices is intended to treat, and the number of affected pediatric patients. Section 515A also allows the Secretary to conclude that adult data can be used to support a reasonable assurance of effectiveness in pediatric subpopulations, as appropriate. The section also requires the Secretary to report annually to relevant congressional committees, specified information about pediatric devices approved in the preceding year.

PMDSIA creates one set of incentives for manufacturers to create pediatric medical devices by making some modifications directly to the HDE. Primarily, PMDSIA exempts some specified manufacturers of pediatric devices from the

[14] The requirements do not attach to premarket notifications, called 510(k)s, which require a demonstration of substantially equivalence to a device already on the market.

general HDE prohibition on selling a device for an amount that exceeds its costs of research and development, fabrication, and distribution. The exemption extends only to specified requests submitted on or before October 1, 2012. PMDSIA gives the Secretary specified pricing-exemption related enforcement and inspection authorities, and creates reporting requirements for adverse events related to devices that qualify for the pricing exemption. The law also requires the Comptroller General to submit a report to relevant congressional committees on the impact of the pricing exemption.

Regarding funding for research on pediatric medical devices, the PMDSIA requires the Secretary to establish a demonstration project to promote pediatric device development. The law authorizes $6 million per year for FY2008 through FY2012 to support the demonstration grants and related activities. The law also requires the National Institutes of Health (NIH) Director to designate a contact point to help pediatric medical device developers locate funding. In addition, it requires the Secretary to submit a plan for expanding pediatric medical device research and development to relevant congressional committees.

Finally, the PMDSIA incorporates certain postmarket surveillance measures related to pediatric medical devices. It expands the conditions under which the Secretary may require postmarket studies as a condition of approval for class II or III devices[15] to include devices expected to have significant use in pediatric subpopulations. These studies may exceed the general 36-month limitation in duration if necessary to assess the impact of the device on pediatric populations' growth and development. The PMDSIA also includes a related dispute resolution provision, entitling a manufacturer to request a review, during which the device may not be deemed misbranded except as necessary to protect public health.

[15] Class II and III medical devices are those that require safety controls.

Table 5. Comparison of *Pediatric Medical Device Safety and Improvement Act of 2007 (FDAAA Title III)* with Previous Law

Topic	Previous Law	FDAAA Title III
New Devices	No provision.	Applicants under FFDCA 515 or 520(m) are to include, if readily available, a description of any pediatric subpopulations that suffer from the condition the device is intended to treat, and the number of affected pediatric patients. [FDAAA 302; FFDCA 515A(a)(1),(2); 21 USC 351 et seq.]
Annual Report	No provision.	The Secretary is to submit an annual report to the Committee on Health, Education, Labor and Pensions (HELP), and the House Committee on Energy and Commerce, that includes, for the preceding year: (1) the number of devices approved for which a pediatric subpopulation suffers from the disease or condition the device is intended to treat; (2) the number of devices labeled for pediatric use; (3) the number of approved pediatric devices exempted from a fee pursuant to pediatric conditions of use; and (4) the review times for applications described above. [FDAAA 302; FFDCA 515A(a)(3); 21 USC 351 et seq.]
Determination of Pediatric Effectiveness and Subpopulation Extrapolation	No provision.	The Secretary may conclude that adult data can be used to support a reasonable assurance of effectiveness in pediatric subpopulations, as appropriate. A study for each pediatric subpopulation may not be necessary if data from one could be extrapolated to another. [FDAAA 302; FFDCA 515A(b),(c); 21 USC 351 et seq.]

Topic	Previous Law	FDAAA Title III
Modification to Humanitarian Device Exemption	A person granted an HDE is not permitted to sell the device for an amount that exceeds the costs of research and development, fabrication, and distribution of the device. [FFDCA 520(m)(3)]	
		The general prohibition remains, but a person granted an HDE is permitted to sell the device for an amount that exceeds the costs of research and development, fabrication, and distribution of the device if the following criteria are met: (1) the device is intended to treat and is labeled for use in a pediatric subpopulation; (2) the device was not approved for pediatric use prior to the act's date of enactment; (3) the number of devices distributed does not exceed a distribution number specified by the Secretary that may not exceed the number specified by the Secretary for the HDE; (4) the applicant immediately notifies the Secretary if the number of devices distributed exceeds the allowable annual distribution number; and (5) the request is submitted on or before October 1, 2012. [FDAAA 303(a); FFDCA 520(m)(3),(5),(6)(A); 21 USC 360j(m)]
Pediatric HDE Inspection	No provision.	The Secretary may inspect the records relating to the number of devices distributed during any calendar year for any person granted an HDE exemption from effectiveness requirements under the new pediatric rule. [FDAAA 303(a); FFDCA 520(m)(6)(B); 21 USC 360j(m)]
Pediatric HDE Modification	No provision.	A person may petition the Secretary to change, and the Secretary may modify, up to 4,000, the number of devices sold under the new pediatric HDE. [FDAAA 303(a); FFDCA 520(m)(6)(C); 21 USC 360j(m)]
HDE Enforcement	No provision.	If the Secretary discovers through notification or inspection that the number of devices marketed exceeded the projected annual distribution number, the HDE pricing restriction will apply from that point forward. [FDAAA 303(a); FFDCA 520(m)(6)(D); 21 USC 360j(m)]

Topic	Previous Law	FDAAA Title III
Definition of *Pediatric Patients* and *Pediatric Subpopulation*	No provision.	For purposes of the HDE, *pediatric patients* means patients who are 21 years of age or younger at the time of diagnosis or treatment. For purposes of the HDE and FFDCA 515A, *pediatric subpopulation* has the same meaning as in FFDCA 520(m)(6)(E)(ii), i.e., neonates, infants, children, or adolescents. [FDAAA 302, 303(a); FFDCA 515,520(m)(6)(E); 21 USC 351,360j(m)]
Adverse Event Reporting, Review of Reports	During the one-year period beginning on the date on which a drug received a period of market exclusivity under FFDCA 505A, any report of an adverse event regarding the drug that the Secretary receives is to be referred to the Office of Pediatric Therapeutics (OPT). [BPCA 17(b)]	
		The drug adverse event requirements remain in effect, and the Secretary is required to report adverse events regarding devices exempt from the HDE price prohibition to the OPT. OPT Director is to provide a periodic review of the reports by the Pediatric Advisory Committee, obtain the Committee's recommendations, and report back to the Secretary. OPT is also to provide for an annual review by the Committee of all devices granted the pediatric HDE, to ensure that the exemption remains appropriate. [FDAAA 303(a); FFDCA 520(m)(7),(8); 21 USC 360j(m)]
Comptroller General Report	No provision.	By January 1, 2012, the Comptroller General is to submit a report to the Senate HELP and House Energy and Commerce Committees on the impact of the new pediatric HDE pricing exemption. [FDAAA 303(b)]
Guidance	No provision.	Within 180 days of enactment, the Commissioner must issue guidance for institutional review committees on how to evaluate requests for approval for devices for which an HDE has been granted. [FDAAA 303(c); 21 USC 360 note]
Point of Contact for Available Funding	No provision.	NIH Director is required to designate a point of contact or office to help innovators and physicians identify some sources of funding available for pediatric medical device development. [FDAAA 304; PHSA 402(b)(23); 42 USC 282(b)]

Topic	Previous Law	FDAAA Title III
Plan for Pediatric Medical Device Research	No provision.	Not later than 180 days after enactment, the Secretary, acting through the Commissioner, in collaboration with the Directors of NIH and the Agency for Healthcare Research and Quality, is required to submit to the Senate HELP and House Energy and Commerce Committees a plan for expanding pediatric medical device research and development. [FDAAA 304(b)]
Demonstration Grants for Improving Pediatric Device Availability	No provision.	The Secretary is required to establish a demonstration project to promote pediatric device development. Grants are to help connect innovators with manufacturers, manage the device development process, guide innovators to federal resources, and provide business assistance. Consortia receiving grants are required to coordinate with points of contact at NIH and FDA. Grantees are also required to report their effectiveness, impact, and device development status to the Secretary annually. For the demonstration grants, $6 million per year is authorized from FY2008 through FY2012. [FDAAA 305; 42 USC 282 note]
OPT and Pediatric Advisory Committee	The duties of FDA's OPT and Pediatric Advisory Committee were restricted to drug-related activities. [P.L. 107-109, 17(b)]	The duties of FDA's OPT are expanded to include increasing pediatric access to medical devices. [FDAAA 306; 21 USC 393a(b); 42 USC 284m note]
Postmarket Surveillance	The Secretary may require, by order, that a manufacturer conduct postmarket surveillance as a condition of approval for any class II or class III device the failure of which would be reasonably likely to have serious adverse health consequences or which is intended to be — (1) implanted in the human body for more than one year, or (2) a life-sustaining or life-supporting device used outside a device user facility.	The Secretary may require, by order or as a condition of approval, that a manufacturer conduct postmarket surveillance for any class II or class III device — (i) the failure of which would be reasonably likely to have serious adverse health consequences; (ii) that is expected to have significant use in pediatric subpopulations; or (iii) that is intended to be (I) implanted in the human body for more than one year, or (II) a life-sustaining or life-supporting device used outside a device user facility. [FDAAA 307; FFDCA 522(b); 21 USC 360l]
	Postmarket surveillance studies required under the section may be a maximum of 36 months in duration. [FFDCA 522(b)]	

Topic	Previous Law	FDAAA Title III
		The general 36-month limitation still applies; however the Secretary may require, as a condition of approval, postmarket studies of longer than 36 months for devices that are expected to have a significant use in pediatric populations, if the extended time is necessary to assess the safety of the device. [FDAAA 307; FFDCA 522(b); 21 USC 360l]
Dispute Resolution	The Secretary is required to provide a procedure for a timely review by an appropriate scientific advisory panel or advisory committee, regarding any obligation concerning drugs or devices under FFDCA or PHSA 351 over which there is a scientific controversy between the Secretary and a person who was a sponsor, applicant, or manufacturer. [FFDCA 562; 21 USC 360bbb-1]	
		In addition to previous rights of review, a manufacturer may also request a review under FFDCA 562 (dispute resolution) of any order or condition requiring postmarket surveillance under this section, during which time the device shall not be deemed adulterated, misbranded, or otherwise in violation of approval or clearance unless necessary to protect public health. [FDAAA 307; FFDCA 522(c); 21 USC 360l]

Title IV. Pediatric Research Equity Act of 2007

FDA has approved for adult use many products never tested in children. Yet clinicians often prescribe them for children believing that the safety and effectiveness demonstrated with adults would hold for younger patients. However, this off-label prescribing can result in children receiving products that do not work for them, or receiving too much or too little of a potentially useful drug. Studies show that, depending on the maturation and development of a child's organs and other factors, some drugs vary in how long they stay in the body, affecting their usefulness. Some side effects are unique to children or children of specific ages, including effects on growth and development.[16]

Recognizing the obstacles (which could be economic, ethical, legal, or mechanical) that make manufacturers reluctant to conduct research to address these questions, FDA and Congress developed two approaches to facilitate pediatric research. FDAAA continues both programs. The first, the Pediatric Research Equity Act (FDAAA Title IV, discussed in this section) is a mandatory program that requires pediatric assessments as part of every new application regarding a new ingredient, indication, dosage form, dosing regimen, or route of administration. The second, the Best Pharmaceuticals for Children Act (FDAAA Title V, discussed in the following section of this report) is voluntary, offering a six-month marketing exclusivity for a product in return for pediatric studies.

For further information, see CRS Report RL33986, *FDA's Authority to Ensure That Drugs Prescribed to Children Are Safe and Effective*, by Susan Thaul.

In 1998, FDA published the Pediatric Rule, which mandated that manufacturers submit pediatric testing data, referred to as a *pediatric assessment*, at the time of all new drug applications. In 2002, a federal court declared the rule invalid, holding that FDA lacked the statutory authority to promulgate it.[17] Congress gave FDA that authority with the enactment of the Pediatric Research Equity Act of 2003 (PREA; P.L. 108-155). PREA requirements cover all drug and biological product applications or supplements to applications concerning a new active ingredient, new indication, new dosage form, new dosing regiment, or new route of administration. The Act includes provisions for deferrals and waivers. PREA also authorizes the Secretary to require the sponsor of an already approved and marketed drug or biological product to submit a pediatric assessment based on criteria described in the law.

The Pediatric Research Equity Act of 2007, Title IV of FDAAA, reauthorizes PREA, amending it to strengthen standards for required tests, explanation of deferrals, labeling, and publicly accessible information. PREA now requires the

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[16] William Rodriguez, Office of New Drugs, FDA, "What We Learned from the Study of Drugs Under the Pediatric Initiatives," June 2006 presentation to the Institute of Medicine, at [http://www.fda.gov/oc/opt/presentations/whatwelearned.ppt].

[17] See Association of Am. Physicians and Surgeons, Inc. v. United States Food and Drug Admin., 2002 U.S. Dist. LEXIS 19689 (October 17, 2002).

Secretary to establish an internal committee, composed of FDA employees with specified expertise, to participate in the review of pediatric plans and assessments, deferrals, and waivers. The law requires the Secretary to track assessments and labeling changes and to make that information publicly accessible; establishes a dispute resolution procedure, which allows the Commissioner, after specified steps, to deem a drug to be misbranded if a manufacturer refuses to make a requested labeling change; and includes review and reporting reporting requirements for adverse events.

PREA requires reports from both the Institute of Medicine (IOM) and the Government Accountability Office (GAO). It also continues to link the program's authorization to the five-year authority FDAAA provides to the pediatric exclusivity program. (See discussion of FDAAA Title V in the next section of this report.)

Table 6. Comparison of *Pediatric Research Equity Act of 2007 (FDAAA Title IV)* with Previous Law

Topic	Previous Law	FDAAA Title IV
Authority Regarding New Drugs and Biological Products	A person submitting an application (or a supplement to an application) to market a drug or biologic with a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration must submit with the application a pediatric assessment. [FDAAA 402(a); FFDCA 505B(a)(1); 21 USC 355c]	
		The reauthorizing law specifies that this Act applies to applications submitted on or after the date of FDAAA's enactment. [FDAAA 402(a); FFDCA 505B(a)(1); 21 USC 355c]
	The assessments must contain data, gathered using appropriate formulations *for each age group* for which the assessment is required, that are adequate to assess the safety and effectiveness of the drug or the biological product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the drug or the biological product is safe and effective. [FDAAA 402(a); FFDCA 505B(a)(2); 21 USC 355c]	
	If the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, FDAAA authorizes the Secretary to judge pediatric effectiveness based on *extrapolation* from adequate and well-controlled studies in adults, usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies. A study may not be needed in each pediatric age group if data from one age group can be extrapolated to another age group. [FDAAA 402(a); FFDCA 505B(a)(2)(B); 21 USC 355c]	
		A review for an application must include a brief *documentation* of data that support the extrapolation conclusions. [FDAAA 402(a); FFDCA 505B(a)(2); 21 USC 355c]
Authority Regarding Already Marketed Drugs and Biological Products	The Secretary may (by order in the form of a letter) require the holder of an approved drug application or biologics license to submit by a specified date the required assessments. [FDAAA 402(a); FFDCA 505B(b)(1); 21 USC 355c]	
		FDAAA specifies that the Secretary's letter requiring assessments of an approved drug must refer to a declined written request for pediatric exclusivity related studies (under FFDCA 505A) for a labeled indication and that the written request was not referred to the Foundation of the NIH for pediatric studies. It also expands "holder" to "sponsor or holder." [FDAAA 402(a); FFDCA 505B(b)(1); 21 USC 355c]
	To do so, the Secretary must find that: [FDAAA 402(a); FFDCA 505B(b)(1); 21 USC 355c]	

Topic	Previous Law	FDAAA Title IV
	(A) the drug or biological product is used for a substantial number of pediatric patients for the labeled indications; and the *absence* of adequate labeling could pose *significant risks* to pediatric patients;	(A) the drug or biological product is used for a substantial number of pediatric patients for the labeled indications; and the *presence* of adequate pediatric labeling "could confer a *benefit* on pediatric patients;" [FDAAA 402(a); FFDCA 505B(b)(1)(A); 21 USC 355c]
	or (B) there is reason to believe that the drug or biological product would represent a meaningful therapeutic benefit over existing therapies for pediatric patients for one or more of the claimed indications; and the *absence* of adequate labeling could pose *significant risks* to pediatric patients.	or (B) there is reason to believe that the drug or biological product would represent a meaningful therapeutic benefit over existing therapies for pediatric patients for one or more of the claimed indications; [FDAAA 402(a); FFDCA 505B(b)(1)(B); 21 USC 355c]
	[Clause did not appear independently of the other two findings.]	or (C) the *absence* of adequate labeling could pose *a risk* to pediatric patients. [FDAAA authorizes the Secretary to act based on this independently of the previous two types of finding.] [FDAAA 402(a); FFDCA 505B(b)(1)(C); 21 USC 355c]
Deferrals	For a new drug or biological product, the Secretary may defer submission of some or all required assessments until a specified date after approval of the drug or issuance of the license for a biological product upon finding that the drug or biological product is ready for approval for use in adults before pediatric studies are complete; pediatric studies should be delayed until additional safety or effectiveness data have been collected; or there is another appropriate reason for deferral. The applicant must also submit to the Secretary certification of the grounds for deferring the assessments; a description of the planned or ongoing studies; and evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time. [FDAAA 402(a); FFDCA 505B(a)(3); 21 USC 355c]	
	No provision.	An applicant must include a *timeline* for the completion of such studies. FDAAA requires an *annual review* of each approved deferral, for which the applicant must submit to the Secretary detailed information on its progress in conducting pediatric studies or, if no progress has been made, evidence of documentation that such studies will be conducted with due diligence and at the earliest possible time. It also requires that all information submitted as part of this annual review be promptly made available to the *public*, including through the FDA website. [FDAAA 402(a); FFDCA 505B(a)(3); 21 USC 355c]

Topic	Previous Law	FDAAA Title IV
Waivers	**Full waiver.** At the request of an applicant (or, for a new drug or biological product, on the initiative of the Secretary), the Secretary shall grant a full waiver, as appropriate, of the requirement to submit assessments under this subsection if the applicant certifies and the Secretary finds that (1) necessary studies are impossible or highly impracticable (because, for example, the number of patients in that age group is so small or patients in that age group are geographically dispersed); or (2) there is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in all pediatric age groups. [FDAAA 402(a); FFDCA 505B(a)(4)(A) and 505B(b)(2)(A); 21 USC 355c]	
	Partial waiver. At the request of an applicant (or, for a new drug or biological product, on the initiative of the Secretary), the Secretary shall grant a partial waiver, as appropriate, of the requirement to submit assessments under this subsection with respect to a specific pediatric age group if the applicant certifies and the Secretary finds that: (1) necessary studies are impossible or highly impracticable; (2) there is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in that age group; (3) the drug or biological product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group, is not likely to be used in a substantial number of pediatric patients in that age group, and (for a marketed drug or biological product) the absence of adequate labeling could not pose significant risks to pediatric patients; or (4) the applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed. [FDAAA 402(a); FFDCA 505B(a)(4)(B) and 505B(b)(2)(B); 21 USC 355c]	
	If a waiver is granted on the grounds that it is not possible to develop a pediatric formulation, the waiver shall cover only the pediatric groups requiring that formulation. [FDAAA 402(a); 505B(b)(2)(C); 21 USC 355c]	
		An applicant seeking a full or partial waiver must submit to the Secretary *documentation* detailing why a pediatric formulation cannot be developed. If a waiver is granted, the applicant's submission must promptly be made *public*, including through posting on the FDA website. [FDAAA 402(a); FFDCA 505B(a)(4)(C) and 505B(b)(2)(C); 21 USC 355c]
Labeling	If the Secretary grants a full or partial waiver because there is evidence that a drug or biological product would be ineffective or unsafe in pediatric populations, the information shall be included in the labeling for the drug or biological product. [FDAAA 402(a); FFDCA 505B(a)(4)(D) and 505B(b)(2)(D); 21 USC 355c]	

Topic	Previous Law	FDAAA Title IV
Relationship to Other Pediatric Provisions	To require a sponsor to submit a pediatric assessment of an approved drug or licensed biological product, the Secretary must have (1) issued a written request for a study, (2) received no agreement to the study from the drug's sponsor, and (3) certified that neither the program for pediatric studies of drugs (at NIH under PHSA 409I) or the Foundation for the NIH (FNIH, under PHSA 499) had sufficient funds to conduct the study, or certified in the Federal Register that no contract or grant had been awarded under those programs although funds were available. After determining that no holder will agree to the written request, the Secretary shall certify whether the Secretary has sufficient funds to conduct the study, taking into account the prioritization under PHSA 409I.	This paragraph regarding the Secretary's requiring the holder of a approved application for a drug or biological product to conduct pediatric studies no longer appears in FFDCA 505B. *[FDAAA (Title V) places an altered version in FFDCA 505A. If the holder declines a written request for a pediatric study and the Secretary continues to determine there is a need for such a study, the Secretary is now required to determine whether FNIH has sufficient funds (no mention is made of the NIH program for pediatric studies of drugs in this context). If funds are available, the Secretary must refer studies to FNIH and FNIH must fund them. If FNIH does not have sufficient funds, the Secretary may require that the holder of the approved application conduct the studies under PREA (FFDCA 505B). [FDAAA 502(a); FFDCA 505A(n)(1)(A); 21 USC 355a]]*
Disclosure of Confidential Information		Regarding requests for studies of approved products or the dissemination of pediatric information following a completed pediatric assessment, FDAAA states it does not alter or amend sections of U.S. Code titles regarding Food and Drugs, Government Organization and Employees, or Crimes and Criminal Procedure regarding the disclosure of confidential information. [FDAAA 402(a); FFDCA 505B(b)(3) and 505B(h)(3); 21 USC 355c]
Meaningful Therapeutic Benefit	The law defined "meaningful therapeutic benefit over existing therapies" as when: (1) the drug or biological product would represent a significant improvement in the treatment, diagnosis, or prevention of a disease, compared with marketed products adequately labeled for that use in the relevant pediatric population; or (2) the drug or biological product is in a class of products or for an indication for which there is a need for additional options. [FDAAA 402(a); FFDCA 505B(c); 21 USC 355c]	
	The law based the assessment on the Secretary's estimation.	FDAAA changes "the Secretary estimates" to "the Secretary determines." [FDAAA 402(a); FFDCA 505B(c); 21 USC 355c]

Topic	Previous Law	FDAAA Title IV
Misbranding	A drug or biological product may be considered misbranded and subject to relevant enforcement action solely for the failure to submit a required assessment or to request approval of a pediatric formulation in accordance with applicable provisions of this section. However, the law does not allow enforcement action under the penalty (imprisonment or fines) authority of this title; and does not allow the failure to submit the assessment or request to be the basis for a proceeding to withdraw approval for a drug or to revoke the license for a biological product. [FDAAA 402(a); FFDCA 505B(d); 21 USC 355c]	
Meeting with Sponsor	Requires that the Secretary, before and during the investigational process for a new drug or biological product, meet with the sponsor of the new drug or biological product to discuss information that the sponsor submits on plans and timelines for pediatric studies; or any planned request by the sponsor for waiver or deferral of pediatric studies. [FDAAA 402(a); FFDCA 505B(e); 21 USC 355c]	
Internal Committee	No provision.	The Secretary must establish an internal committee, composed of FDA employees with specified expertise, to participate in the review of pediatric plans, assessments, deferrals, and waivers. [FDAAA 403; FFDCA 505C; 21 USC 355d] (Note: This is the same internal committee to which FDAAA 502(a) [FFDCA 505A(f); 21 USC 355a] refers; see next section.) The Secretary must document the internal committee's activity, track pending assessments, and place the information on the FDA website for easy public access. The internal committee must conduct a retrospective review and analysis of assessments, deferrals, and waivers to the Secretary, who would be required to issue recommendations for improvements. [FDAAA 402(a); FFDCA 505B(f); 21 USC 355c]
Review of Pediatric Plans, Assessments, Deferrals, and Waivers	No provision.	The review must include analysis of the quality and consistency of pediatric information in pediatric assessments and the appropriateness of waivers and deferrals granted. The Secretary must, based on such review, issue recommendations to the review divisions for improvements and initiate guidance to industry. The Secretary must, in consultation with the internal committee, track and make available to the public specified statistics on the numbers of assessments, study designs, deferral and waiver requested and granted, pediatric formulations developed, labeling changes, etc. The report must include the reasons for each of those events not happening. [FDAAA 402(a); FFDCA 505B(f); 21 USC 355c]

Topic	Previous Law	FDAAA Title IV
Dispute Resolution	No provision.	FDAAA establishes a dispute resolution procedure for when a sponsor does not agree with the Commissioner's request for a label change. In those cases, it requires the Commissioner to refer the dispute to the Pediatric Advisory Committee for review and recommendation. If the sponsor continues to disagree with a requested labeling change, the Commissioner may deem the drug to be misbranded. The Commissioner must refer the dispute to the Pediatric Advisory Committee within 30 days of a sponsor's disagreeing to change the label. Nothing in this subsection shall preclude, delay, or serve as the basis to stay other courses of action via the Pediatric Advisory Committee process or an enforcement action under this Act. [FDAAA 402(a); FFDCA 505B(g)(1); 21 USC 355c]
Labeling to Include Secretary's Determination	No provision.	Upon making a determination that a pediatric assessment does or does not demonstrate that the subject drug is safe and effective in pediatric populations or subpopulations, including whether such assessment results are inconclusive, the Secretary must order the label to include information about those results and a statement of the Secretary's determination. [FDAAA 402(a); FFDCA 505B(g)(2); 21 USC 355c]
Dissemination of Pediatric Information	No provision.	The Secretary must make available to the public in an easily accessible manner, including by posting on the FDA website, the medical, statistical, and clinical pharmacology reviews of a submitted pediatric assessment. The Secretary must require the sponsor of an assessment that results in certain labeling changes to distribute such information to health care providers. [FDAAA 402(a); FFDCA 505B(h); 21 USC 355c]
Adverse Event Reporting	No provision.	Following a labeling change, the Secretary must refer all adverse event reports to the Office of Pediatric Therapeutics (OPT). For the first year after the change, the OPT director must provide for their review by the Pediatric Advisory Committee (PAC) and obtain its recommendations for action by the Secretary. In subsequent years, the OPT director may refer the adverse event reports to the PAC. FDAAA states that these requirements "shall supplement, not supplant, other review of such adverse event reports by the Secretary." [FDAAA 402(a); FFDCA 505B(i); 21 USC 355c]
Orphan Drugs	Unless the Secretary requires otherwise by regulation, this section does not apply to any drug for an indication for which orphan designation has been granted under this title. [FDAAA 402(a); FFDCA 505B(k); 21 USC 355c]	

Topic	Previous Law	FDAAA Title IV
Institute of Medicine Study	No provision.	FDAAA requires that the Secretary contract with the IOM to conduct a study and report to Congress regarding pediatric studies and resulting labeling changes. It directs that the IOM review and assess, using a representative sample of studies, the use of extrapolation, alternative endpoints, neonatal assessment tools, number and type of pediatric adverse events, and ethical issues in pediatric clinical trials. [FDAAA 402(a); FFDCA 505B(l); 21 USC 355c]
Government Accountability Office Report	No codified provision.	FDAAA requires a GAO report, in consultation with the Secretary, to Congress by January 1, 2011, that addresses the effectiveness of FFDCA 505A and 505B and PHSA 409I in ensuring that medicines used by children are tested and properly labeled. It specifies required elements of that report. FDAAA does not indicate that this provision be placed within the U.S. Code. [FDAAA 404; not in FFDCA or USC]
Reference to Sunset	The authority under this section shall remain in effect so long as an application subject to this section may be accepted for filing by the Secretary on or before the date specified in the market exclusivity for pediatric studies of drugs section of this title. [FDAAA 402(a); FFDCA 505B(m); 21 USC 355c]	

Title V. Best Pharmaceuticals for Children Act of 2007

Title V of FDAAA reauthorizes and changes legislation first passed in 1997. As part of the FDA Modernization Act of 1997 (P.L. 105-115), Congress provided drug manufacturers with a financial incentive to conduct pediatric use studies on their patented products. The "Pediatric Studies of Drugs" provision provided that if a manufacturer complied with a written FDA request for a specific pediatric study, FDA would add six months to its market exclusivity for that product.[18] This tool is the second approach that FDA and Congress have taken to encouraging pediatric drug research, the other, required pediatric assessments of new products, is discussed in the preceding section of this report regarding FDAAA Title IV.

For further information, see CRS Report RL33986, *FDA's Authority to Ensure That Drugs Prescribed to Children Are Safe and Effective*, by Susan Thaul.

In 2002, the Best Pharmaceuticals for Children Act (BPCA 2002; P.L. 107-109) reauthorized the exclusivity provisions for another five years. It also added provisions to encourage pediatric research of products that were no longer covered by patent or other marketing exclusivity agreements, to which pediatric exclusivity was not relevant. It required the Secretary to list those *off-patent* products for which pediatric studies are needed to assess safety and effectiveness. It also established an off-patent research fund at NIH (PHSA 409I) and authorized appropriations of $200 million for FY2002 and such sums as are necessary for each of the five years until the provisions were set to sunset on October 1, 2007.

For *on-patent* drugs whose manufacturers declined FDA's written requests for studies (and, therefore, exclusivity), BPCA 2002 amended FFDCA 505A to allow FDA to refer drugs needing pediatric studies to the Foundation for the NIH (FNIH, PHSA 499), creating a second program of FDA-NIH collaboration.[19]

Other provisions in the 2002 BPCA included giving priority status to pediatric supplemental applications; the establishment of an FDA Office of Pediatric Therapeutics (OPT); the definition of pediatric age groups to include neonates; and a direction to the Secretary to contract with the IOM for a review of regulations, federally prepared or supported reports, and federally supported evidence-based research, all relating to clinical research involving children. The IOM report to

[18] During that six-month period, FDA would not grant marketing approval to another identical product (usually a generic).

[19] The Foundation supports the research mission of NIH using public-private partnerships; see [http://www.fnih.org/aboutus/aboutus.shtml].

Congress was also to include recommendations on best practices relating to research involving children.[20]

Title V of FDAAA again reauthorizes the pediatric exclusivity program, amending FFDCA 505A to sunset on October 1, 2012. It also encourages research on off-patent products, strengthens the requirements for labeling changes based on the results of pediatric use studies, and provides for the reporting of adverse events.

FDAAA authorizes the Secretary to grant additional marketing exclusivity, for both new drugs and drugs already on the market, only after a sponsor has completed and reported on the studies that the Secretary has requested in writing, including appropriate formulations of the drug for each age group of interest, and after any appropriate labeling changes are approved, all within the agreed upon time frames. An applicant who turns down a request on the grounds that developing appropriate pediatric formulations of the drug is not possible must provide evidence to support that claim.

The new law requires that the sponsor propose pediatric labeling resulting from the studies. For a product studied under this section, the labeling must include study results and the Secretary's determination whether those results demonstrate the drug's safety and effectiveness (if the results do or do not indicate safety and effectiveness, or if they are inconclusive). The product sponsor must disseminate labeling change information to health care providers, and the Commissioner must report to the Secretary on the review of all adverse event reports and recommendations on actions in response. Other provisions of the law set time frames for the actions it requires.

Public notice requirements are expanded beyond the current notice of an exclusivity decision to include copies of the written request. The Secretary must also publicly identify any drug with a developed pediatric formulation that studies had demonstrated to be safe and effective for children that an applicant has not introduced onto the market within one year.

A new dispute resolution process includes referral to the Pediatric Advisory Committee. The internal review committee, which FDAAA Title IV requires the Secretary to establish, must review all written requests. The Secretary, with that committee, must track all pediatric studies and labeling changes according to specified questions.

Other provisions require applicants to submit, along with the report of requested studies, all postmarket adverse event reports regarding that drug; refine study scope to allow the Secretary to include preclinical studies; and except from exclusivity any drug with another exclusivity that is to expire in less than nine months.

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[20] See IOM, *Ethical Conduct of Clinical Research Involving Children*, Committee on Clinical Research Involving Children (Washington, DC: National Academies Press, 2004), done with funding from NIH and FDA.

FDAAA amends PHSA Section 409I (as discussed earlier), which required that the Secretary, through the NIH Director and in consultation with the Commissioner and pediatric research experts, list approved drugs for which pediatric studies are needed to assess safety and effectiveness. It changes the specifications from an annual list of approved drugs to a list, revised every three years, of priority study needs in pediatric therapeutics, including drugs or indications.

If the Secretary determines there is a need for pediatric information for a drug for which pediatric studies have not been completed, the Secretary must either issue a proposal to award a grant to conduct such studies, if funds are available through FNIH, or refer the drug for inclusion on the list established under PHSA Section 409I. FDAAA also requires reports from the IOM and the GAO.

The provisions in Title V of FDAAA make up the following two tables: the first addressing amendments to FFDCA, the second relating to PHSA.

Table 7. Comparison of *Best Pharmaceuticals for Children Act of 2007 (FDAAA Title V, Section 502(a))* with Previous Law

Topic	Previous Law	FDAAA Title V, Section 502(a)
Definition of Studies	As used in this section, the term "pediatric studies" or "studies" means at least one clinical investigation (that, at the Secretary's discretion, may include pharmacokinetic studies) in pediatric age groups (including neonates in appropriate cases) in which a drug is anticipated to be used. [FDAAA 502(a); FFDCA 505A(a); 21 USC 355a]	
		Adds that, at the Secretary's discretion, clinical investigation may include preclinical studies. [FDAAA 502(a); FFDCA 505A(a); 21 USC 355a]
Market Exclusivity for New Drugs	Six-month pediatric exclusivity is granted if, prior to approval of an application that is submitted under section 355(b)(1) of this title, the Secretary determines that information relating to the use of a *new drug* in the pediatric population may produce health benefits in that population, the Secretary makes a written request for pediatric studies (which shall include a timeframe for completing such studies), and such studies are completed within any such timeframe and the reports thereof submitted in accordance with subsection (d)(2) of this section or accepted in accordance with subsection (d)(3) of this section. [FDAAA 502(a); FFDCA 505A(b); 21 USC 355a]	
		Adds that the applicant agrees to the request and that such studies are completed using appropriate formulations for each age group for which the study is requested. [FDAAA 502(a); FFDCA 505A(b)(1); 21 USC 355a]
Market Exclusivity for Already Marketed Drugs	Six-month pediatric exclusivity is granted if the Secretary determines that information relating to the use of an *approved drug* in the pediatric population may produce health benefits in that population and makes a written request to the holder of an approved application under section 355(b)(1) of this title for pediatric studies (which shall include a timeframe for completing such studies), the holder agrees to the request, the studies are completed within any such timeframe, and the reports thereof are submitted in accordance with subsection (d)(2) of this section or accepted in accordance with subsection (d)(3) of this section. [FDAAA 502(a); FFDCA 505A(c); 21 USC 355a]	
		Adds that such studies are completed using appropriate formulations for each age group for which the study is requested. [FDAAA 502(a); FFDCA 505A(c)(1); 21 USC 355a]
Extension of Exclusivity	Extended by six months other exclusivities granted (such as for new drugs, certain generic drugs, drugs for rare diseases or conditions) under the FFDCA. [FDAAA 502(a); FFDCA 505A(b)(1)(B) and 505A(c)(1)(B); 21 USC 355a]	

Topic	Previous Law	FDAAA Title V, Section 502(a)
Exception	No provision.	Adds that the Secretary shall not extend the exclusivity period if the determination is made less than 9 months before the expiration of exclusivity period. [FDAAA 502(a); FFDCA 505A(b)(2) and 505A(c)(2); 21 USC 355a]
Agreement for Studies	The Secretary may, pursuant to a written request and after consultation with the sponsor of an application for an investigational new drug or a new drug, or the holder of an approved application for a drug, agree with the sponsor or holder for the conduct of pediatric studies for such drug. Such agreement shall be in writing and shall include a timeframe for such studies. [FDAAA 502(a); FFDCA 505A(d)(1); 21 USC 355a]	
		Request for studies. Adds that a single written request may relate to more than one use of a drug; and may include uses that are both approved and unapproved. [FDAAA 502(a); FFDCA 505A(d)(1); 21 USC 355a] Combines language relating to new drugs and already approved drugs. Requires the applicant or holder to respond to the Secretary's written request within 180 days, indicating either when studies will be initiated or the reasons for declining the request. [FDAAA 502(a); FFDCA 505A(d)(2); 21 USC 355a]
	No provision.	An applicant or holder who does not agree with the request on the grounds that it is not possible to develop the appropriate pediatric formulation must submit to the Secretary the reasons such pediatric formulations cannot be developed. [FDAAA 502(a); FFDCA 505A(d)(2)(ii); 21 USC 355a]
	No provision.	An applicant or holder who agrees to the request for such studies shall provide the Secretary, at the same time as the submission of the reports of such studies, with all available postmarket adverse event reports regarding the subject drug. [FDAAA 502(a); FFDCA 505A(d)(2)(B); 21 USC 355a]

Topic	Previous Law	FDAAA Title V, Section 502(a)
Representation of Minorities	The law directs the Secretary to take into account adequate representation of children of ethnic and racial minorities. [FDAAA 502(a); FFDCA 505A(d); 21 USC 355a]	
	The Secretary is required to do this in reaching an agreement regarding written protocols.	The Secretary is required to do this "[i]n issuing such a request." [FDAAA 502(a); FFDCA 505A(d)(1); 21 USC 355a]
Determination by Secretary	The Secretary must determine if such studies were or were not conducted in accordance with the original written request and the written agreement and reported in accordance with the requirements of the Secretary for filing, and so notify the sponsor or holder within a specified number of days after the submission of the report of the studies. [FDAAA 502(a); FFDCA 505A(d)(3); 21 USC 355a]	
	If the sponsor or holder and the Secretary agree upon written protocols for the studies, the studies requirement is satisfied upon the completion of the studies and submission of the reports thereof in accordance with the original written request and the written agreement. For agreed upon studies, the Secretary was required to make the determination within 60 days of the report's submission. If the sponsor or holder and the Secretary had not agreed in writing on the protocols for the studies, the requirement for pediatric studies was satisfied when such studies had been completed and the reports accepted by the Secretary. The Secretary was required to accept or reject such reports and so notify the sponsor or holder not later than 90 days after the submission of the reports of the studies.	FDAAA requires that the Secretary make the determination within 180 days of the report's submission. [FDAAA 502(a); FFDCA 505A(d)(3); 21 USC 355a]
	The Secretary's only responsibility in accepting or rejecting the reports shall be to determine whether the studies fairly respond to the written request, have been conducted in accordance with commonly accepted scientific principles and protocols, and have been reported in accordance with the requirements of the Secretary for filing. [FDAAA 502(a); FFDCA 505A(d)(3); 21 USC 355a]	
Written Request to Holders of Approved Applications for Drugs that Have Market Exclusivity	If the Secretary makes a written request for pediatric studies (including neonates, as appropriate) under subsection (c) of this section to the holder of an approved new drug application, the holder, not later than 180 days after receiving the written request, shall respond to the Secretary as to the intention of the holder to act on the request by indicating when the pediatric studies will be initiated, if the holder agrees to the request; or indicating that the holder does not agree to the request.	Addresses requests for studies of both new drugs and already approved drugs together; see above.

Topic	Previous Law	FDAAA Title V, Section 502(a)
Referral if Pediatric Studies Not Completed: No Agreement to Request	The Secretary is required to act if the manufacturer does not agree to a written request within the specified time period, and if the Secretary determines that there is a continuing need for information relating to the use of the drug in the pediatric population (including neonates, as appropriate). [Previous law addressed this in FFDCA 505A(d)(4)(B); and FDAAA 502(a) places it in FFDCA 505A(n); 21 USC 355a]	
	The Secretary was to refer the drug to FNIH, established under 42 USC 290b, for the conduct of the pediatric studies described in the written request.	The Secretary must make the determination whether further study is needed through the internal committee established under FFDCA 505C. Different procedures are specified for drugs with and without current patents.
		For a drug with an unexpired patent, the Secretary must first certify whether FNIH has sufficient funding for the studies in the written request. -If funding is available, requires the Secretary to refer the written request to FNIH, and requires FNIH to fund the studies. -If funding is not available, the Secretary must consider whether to require pediatric assessments under FFDCA 505B(b). [FDAAA 502(a); FFDCA 505A(n)(1)(A); 21 USC 355a] For a drug with no current patent, requires that the Secretary refer the drug for inclusion on the list established under PHSA 409I. [FDAAA 502(a); FFDCA 505A(n)(1)(B); 21 USC 355a]
Public Notice	The Secretary shall give public notice of the name of the drug, the name of the manufacturer, and the indications to be studied made in a referral to the FNIH.	FDAAA deletes this provision and adds: For a drug for which the Secretary decides *not* to require an assessment under FFDCA 505B, the Secretary must give public notice and the basis for that decision. [FDAAA 502(a); FFDCA 505A(n)(2); 21 USC 355a]
Lack of Funds	On referral of a drug under subparagraph (B)(i), FNIH shall issue a proposal to award a grant to conduct the requested studies unless FNIH certifies to the Secretary, within a timeframe that the Secretary determines is appropriate through guidance, that FNIH does not have funds available under PHSA 499 to conduct the requested studies. If FNIH so certifies, the Secretary shall refer the drug for inclusion on the list established under PHSA 409I for the conduct of the studies.	The law was rewritten so that for a drug with an unexpired patent, the Secretary must certify whether the FNIH has sufficient funding to conduct the studies *before* referring a request to FNIH. [FDAAA 502(a); FFDCA 505A(n)(1)(A); 21 USC 355a] It requires the FNIH to fund a study that the Secretary does refer. [FDAAA 502(a); FFDCA 505A(n)(1)(A); 21 USC 355a].

Topic	Previous Law	FDAAA Title V, Section 502(a)
No Requirement to Refer	Nothing in this subsection shall be construed to require that every declined written request shall be referred to FNIH.	No provision.
Written Requests for New Drugs	For a drug for which a written request had not been accepted before marketing approval, if the Secretary determines that there is a continuing need for information relating to the use of the drug in the pediatric population (including neonates, as appropriate), the Secretary shall issue a written request after the date of approval of the drug. [FFDCA 505A(d)(4)(F)]	FDAAA changes how the Secretary would handle a declined request for studies. If a written request is not accepted by the sponsor or holder of an application, and the Secretary does not refer the request to FNIH (under FFDCA 505A(n)(1)(A)), the Secretary may require the holder to submit a pediatric assessment under FFDCA 505B(b)(1). [FDAAA 502(a); FFDCA 505A(n)(1)(A); 21 USC 355a]
Delay of Effective Date for Certain Application	The Secretary shall delay for up to 90 days the approval of a generic or other product whose application relies on safety and effectiveness studies conducted by an entity other than the applicant (such as for a new formulation (under FFDCA 505(b)(2)) or a generic version (under FFDCA 505(j)) until a determination is made regarding pediatric studies under this section (FFDCA 505A). In the event that requirements of this section are satisfied, the applicable six-month marketing exclusivity shall be deemed to have been running during the period of delay.	No provision.
Notice of Determinations on Studies Requirement	The Secretary shall publish a notice of any determination that the requirements for the conduct of pediatric studies have been met and that submissions and approvals under FFDCA 505(b)(2) or (j) [generic] for a drug will be subject to the provisions of this section. [FDAAA 502(a); FFDCA 505A(e)(1); 21 USC 355a]	
		Such notice must be published within 30 days of the Secretary's determination regarding market exclusivity and must include a copy of the written request under subsection (b) or (c). [FDAAA 502(a); FFDCA 505A(e)(1); 21 USC 355a]
	No provision.	The Secretary must publicly identify any drug with a developed pediatric formulation that studies have demonstrated to be safe and effective for children if its sponsor has not introduced the pediatric formulation onto the market within one year. [FDAAA 502(a); FFDCA 505A(e)(2); 21 USC 355a]

Topic	Previous Law	FDAAA Title V, Section 502(a)
Internal Review of Written Requests and Pediatric Studies	No provision.	The internal review committee, which FDAAA 403 requires the Secretary to establish, must review all written requests. It may review studies submitted pursuant to this provision to make recommendations to the Secretary on whether to accept or reject the studies. The Secretary must, in consultation with the internal committee, track pediatric studies and labeling changes; and make available to the public specified information such as types of studies, and drugs and uses studied. [FDAAA 502(a); FFDCA 505A(f); 21 USC355a]
Limitations	A drug to which the six-month period under subsection (b) or (c) of this section has already been applied (1) may receive an additional six-month period under subsection (c)(1)(A)(ii) of this section for a supplemental application if all other requirements under this section are satisfied, except that such a drug may not receive any additional such period under subsection (c)(2) of this section; and (2) may not receive any additional such period under subsection (c)(1)(B) of this section. [FDAAA 502(a); FFDCA 505A(g); 21 USC 355a]	
Relationship to Pediatric Research Requirements	Notwithstanding any other provision of law, if any pediatric study is required by a provision of law (including a regulation) other than this section and such study meets the completeness, timeliness, and other requirements of this section, such study shall be deemed to satisfy the requirement for market exclusivity pursuant to this section. [FDAAA 502(a); FFDCA 505A(h); 21 USC 355a]	
Priority Status for Labeling Changes	Any supplement to an application under FFDCA 505 proposing a labeling change pursuant to a report on a pediatric study under this section shall be considered to be a priority supplement; and shall be subject to the performance goals established by the Commissioner for priority drugs. [FDAAA 502(a); FFDCA 505A(i)(1); 21 USC 355a]	
		This provision now refers to pediatric applications and supplements. [FDAAA 502(a); FFDCA 505A(i)(1); 21 USC 355a]

Topic	Previous Law	FDAAA Title V, Section 502(a)
Labeling Change Dispute Resolution	If, not later than 180 days after the date of submission of the application, the Commissioner determines that there is a disagreement with the sponsor on appropriate changes to the labeling for the drug that is the subject of the application, the Commissioner must request that the sponsor of the application make any labeling change that the Commissioner determines to be appropriate; and if the sponsor of the application does not agree to make a labeling change requested by the Commissioner, the Commissioner shall refer the matter to the Pediatric Advisory Committee. [FDAAA 502(a); FFDCA 505A(i)(2)(A); 21 USC 355a]	
	The law specified that the Commissioner determined that the related application was approvable and that the only open issue is the labeling change.	FDAAA refers to the Commissioner's determining that "the sponsor and the Commissioner have been unable to reach agreement." It also adds that the Commissioner must make the referral if the sponsor does not agree within 30 days of the request. [FDAAA 502(a); FFDCA 505A(i)(2)(A); 21 USC 355a]
	Not later than 90 days after receiving a referral, the Pediatric Advisory Committee shall review the pediatric study reports, and make a recommendation to the Commissioner concerning appropriate labeling changes, if any. The Commissioner shall consider the recommendations of the Pediatric Advisory Committee and, if appropriate, not later than 30 days after receiving the recommendation, make a request to the sponsor of the application to make any labeling change that the Commissioner determines to be appropriate. If the sponsor of the application, within 30 days after receiving a request, does not agree to make a labeling change requested by the Commissioner, the Commissioner may deem the drug that is the subject of the application to be misbranded. Nothing in this subsection limits the authority of the United States to bring an enforcement action under this chapter when a drug lacks appropriate pediatric labeling. Neither course of action (the Pediatric Advisory Committee process or an enforcement action referred to in the preceding sentence) shall preclude, delay, or serve as the basis to stay the other course of action. [FDAAA 502(a); FFDCA 505A(i)(2)(E); 21 USC 355a]	
Secretary's Determination Public	No provision.	The Secretary must, upon determining that a pediatric study conducted under this section does or does not demonstrate that the drug that is the subject of the study is safe and effective, including whether such study results are inconclusive, in pediatric populations or subpopulations, order the labeling of such product to include information about the results of the study and a statement of the Secretary's determination. [FDAAA 502(a); FFDCA 505A(j); 21 USC 355a]

Topic	Previous Law	FDAAA Title V, Section 502(a)
Dissemination of Pediatric Information	Not later than a specified number of days after the date of submission of a report on a pediatric study under this section, the Commissioner shall make available to the public a summary of the medical and clinical pharmacology reviews of pediatric studies conducted for the supplement, including by publication in the Federal Register. [FDAAA 502(a); FFDCA 505A(k)(1); 21 USC 355a]	
	The law allowed up to 180 days.	FDAAA allows up to 210 days. It also substitutes the Secretary for the Commissioner, adds statistical reviews, and refers to studies conducted under subsection (b) or (c). [FDAAA 502(a); FFDCA 505A(k)(1); 21 USC 355a] Requires, for studies that result in labeling changes reflected in the annual summary distribution, that their sponsors distribute, at least annually, such information to health care providers. [FDAAA 502(a); FFDCA 505A(k)(2); 21 USC 355a]
	Regarding dissemination of information of pediatric studies under this section, FDAAA states it does not alter or amend sections of U.S. Code titles regarding Food and Drugs, Government Organization and Employees, or Crimes and Criminal Procedure regarding the disclosure of confidential information. [FDAAA 502(a); FFDCA 505A was (j)(2), now (k)(3); 21 USC 355a]	
Adverse Event Reporting	No provision.	The Secretary must, for the year following a labeling change, ensure referral of all adverse event reports to the OPT, whose director must provide for their review by the Pediatric Advisory Committee and obtain its recommendations for action by the Secretary. In subsequent years, the Secretary must, as appropriate, refer all pediatric adverse event reports for a drug for which a pediatric study was conducted under this section to the OPT, whose director may refer them for review and recommendation to the Pediatric Advisory Committee. FDAAA states that these requirements “shall supplement, not supplant, other review of such adverse event reports by the Secretary.” [FDAAA 502(a); FFDCA 505A(l); 21 USC 355a]
Interaction of Exclusivities	If the generic drug exclusivity period overlaps with the pediatric exclusivity period, the period will be extended by the number of days of the overlap. [FDAAA 502(a); FFDCA 505A(m); 21 USC 355a]	

Topic	Previous Law	FDAAA Title V, Section 502(a)
Prompt Approval of Generic Drugs When Pediatric Information Is Added to Labeling	A drug for which an application has been submitted or approved under an abbreviated new drug application (ANDA, for a generic drug) shall not be considered ineligible for approval under that section or misbranded on the basis that the labeling of the drug omits a pediatric indication or any other aspect of labeling pertaining to pediatric use when the omitted indication or other aspect is protected by patent or by certain exclusivities. *Labeling.* The Secretary may require that the labeling of an approved generic drug (FFDCA 505(j)) that omits a pediatric indication or other required aspect of labeling include: a statement that the product is not labeled for all or specific pediatric uses because of marketing exclusivity held by another manufacturer; and a statement of any appropriate pediatric contraindications, warnings, or precautions that the Secretary considers necessary. FDAAA includes a clause to preserve pediatric exclusivity and other provisions under certain paragraphs of FFDCA 505, 505A, 505(j). [FDAAA 502(a); FFDCA 505A(o); 21 USC 355a]	
Institute of Medicine Study	No provision.	The Secretary must contract, within 3 years of enactment, with the IOM to conduct a study and report to Congress regarding the written requests and studies conducted pursuant to this section. The IOM must review representative requests and studies since 1997 and labeling changes made as a result of such studies; assess the use of extrapolation, alternative endpoints, neonatal assessment tools, and ethical issues in pediatric clinical trials; and review and assess the pediatric studies of biological products; and make recommendations regarding appropriate incentives for encouraging pediatric studies of biologics. [FDAAA 502(a); FFDCA 505A(p); 21 USC 355a]
Secretary's Report to Congress	The Secretary was required to conduct a study of all relevant issues, as specified, and report to Congress, by January 1, 2001, based on the experience under the program established under this section.	No provision.
Sunset	The law provides a sunset date by which all written requests for pediatric studies must be made, applications accepted for filing, and all other requirements met to receive a 6-month marketing exclusivity under this section. [FDAAA 502(a); FFDCA 505A; 21 USC 355a]	
	The sunset date was October 1, 2007.	The sunset date is October 1, 2012. [FDAAA 502(a); FFDCA 505A(q); 21 USC 355a]

Table 8. Comparison of *Best Pharmaceuticals for Children Act of 2007 (FDAAA Title V, Sections 502(b-f) and 503)* with Previous Law

Topic	Previous Law	FDAAA Title V, Sections 502(b-f) and 503
List of Priority Issues in Pediatric Therapeutics	The Secretary, acting through the NIH Director and in consultation with the Commissioner and experts in pediatric research, shall develop, prioritize, and publish an annual list of approved drugs needing additional studies of safety and effectiveness in the pediatric population.	The focus of the list is changed to "a priority list of needs in pediatric therapeutics, including drugs or indications that require study." The Secretary must develop and publish the list not later than one year after enactment, and revise it every three years. [FDAAA 502(b); PHSA 409I(a)(1); 42 USC 284m]
	The criteria for developing and prioritizing the list of drugs included available information, need for information, whether new pediatric studies concerning the drug may produce health benefits in the pediatric population; and whether reformulation of the drug is necessary.	The section refers to a list of needs, rather than a list of drugs. It also replaces the existing criteria with others that give examples within the categories of therapeutic gaps in pediatrics; particular pediatric diseases, disorders or conditions where more complete knowledge and testing of therapeutics may be beneficial in pediatric populations; and the adequacy of necessary infrastructure to conduct pediatric pharmacological research. [FDAAA 502(b); PHSA 409I(a)(2); 42 USC 284m]
Funding of Pediatric Studies and Research	The Secretary shall award contracts to entities that have the expertise to conduct pediatric clinical trials (including qualified universities, hospitals, laboratories, contract research organizations, federally funded programs such as pediatric pharmacology research units, other public or private institutions, or individuals) to enable the entities to conduct pediatric studies concerning one or more drugs identified in the list. [FDAAA 502(b); PHSA 409I(b); 42 USC 284m]	
		The Secretary must act through NIH. The description of entities is expanded to include expertise with clinical trials "or other research"; and practice groups. In addition to contracts, the Secretary may use grants or other appropriate funding mechanisms. [FDAAA 502(b); PHSA 409I(b); 42 USC 284m]

Topic	Previous Law	FDAAA Title V, Sections 502(b-f) and 503
Process for Proposed Pediatric Study Requests and Labeling Changes	No provision.	The NIH Director must submit, as appropriate, proposed pediatric study requests for consideration by the Commissioner for pediatric studies of a specific pediatric indication on the list of priority issues in pediatric therapeutics. The request must include the information required by FFDCA 505A requests. The NIH Director may submit a proposed pediatric study request for a drug for which there is an approved or submitted application under FFDCA Section 505(j); and there is no patent protection or market exclusivity protection for at least one form of the drug under the FFDCA; and additional studies are needed to assess the safety and effectiveness of the use of the drug in the pediatric population. [FDAAA 502(b); PHSA 409I(c)(1); 42 USC 284m]
Written Request to Holders of Approved Applications for Drugs Lacking Exclusivity	The Commissioner, in consultation with the NIH Director, may issue a written request (which shall include a timeframe for negotiations for an agreement) for pediatric studies to all holders of an approved application for the drug under FFDCA 505 [21 USC 355]. Such a written request shall be made in a manner equivalent to the manner in which a written request is made under subsection (a) or (b) of FFDCA 505A [21 USC 355a], including with respect to information provided on the pediatric studies to be conducted pursuant to the request. [FDAAA 502(b); PHSA 409I(c)(2); 42 USC 284m]	
	The written request referred to a study of a drug identified in the list of drugs for which pediatric studies are needed.	The written request refers to a study of an indication or indications submitted pursuant to the list of priority issues in pediatric therapeutics. Studies must use appropriate formulations for each age group for which the study is requested. [FDAAA 502(b); PHSA 409I(c)(2); 42 USC 284m]
Requests for Contract Proposals	If the Commissioner does not receive a response to a written request within 30 days of the date on which a request was issued, or if a referral is made, the Secretary, acting through the NIH Director and in consultation with the Commissioner, shall publish a request for contract proposals to conduct the pediatric studies described in the written request. [FDAAA 502(b); PHSA 409I(c)(3); 42 USC 284m]	
		The Secretary must publish the request if the Commissioner has not received a response to a written request within 30 days. [FDAAA 502(b); PHSA 409I(c)(3); 42 USC 284m]
Disqualification	A holder that receives a first right of refusal shall not be entitled to respond to a request for contract proposals. [FDAAA 502(b); PHSA 409I(c)(4); 42 USC 284m]	
Guidance	Not later than 270 days after January 4, 2002, the Commissioner shall promulgate guidance to establish the process for the submission of responses to written requests.	No provision.

Topic	Previous Law	FDAAA Title V, Sections 502(b-f) and 503
Funding	A contract under this section may be awarded only if a proposal for the contract is submitted to the Secretary in such form and manner, and containing such agreements, assurances, and information as the Secretary determines to be necessary to carry out this section. [FDAAA 502(b); PHSA 409I(c)(5); 42 USC 284m]	
		The Secretary may allow grants or other funding in addition to contracts. [FDAAA 502(b); PHSA 409I(c)(5); 42 USC 284m]
Reporting of Studies	On completion of a pediatric study in accordance with a contract awarded under this section, a report concerning the study shall be submitted to the NIH Director and the Commissioner. The report shall include all data generated in connection with the study. [FDAAA 502(b); PHSA 409I(c)(6)(A); 42 USC 284m]	
		The section refers to "an award" rather than "a contract." It also requires that the report include the written request. [FDAAA 502(b); PHSA 409I(c)(6)(A); 42 USC 284m]
Availability of Reports	Each report submitted shall be considered to be in the public domain (subject to FFDCA 505A(d)(4)(D) [21 USC 355a (d)(4)(D)]) and shall be assigned a docket number by the Commissioner. An interested person may submit written comments concerning such pediatric studies to the Commissioner, and the written comments shall become part of the docket file with respect to each of the drugs.	
Action by Commissioner	The Commissioner shall take appropriate action in response to the reports. [FDAAA 502(b); PHSA 409I(c)(6)(B,C); 42 USC 284m]	
Requests for Labeling Change	During the 180-day period after the date on which a report is submitted, the Commissioner must review the report and such other data as are available concerning the safe and effective use in the pediatric population of the drug studied; and negotiate with the holders of approved applications for the drug studied for any labeling changes that the Commissioner determines to be appropriate and requests the holders to make. The Commissioner must place in the public docket file a copy of the report and of any requested labeling changes; and publish in the Federal Register a summary of the report and a copy of any requested labeling changes. [FDAAA 502(b); PHSA 409I(c)(7)(A,B,C); 42 USC 284m]	
		The Commissioner must also post information on the FDA website. [FDAAA 502(b); PHSA 409I(c)(7)(C); 42 USC 284m]

Topic	Previous Law	FDAAA Title V, Sections 502(b-f) and 503
Dispute Resolution	If, not later than the end of the 180-day period specified, the holder of an approved application for the drug involved does not agree to any labeling change requested by the Commissioner under that paragraph, the Commissioner shall refer the request to the Pediatric Advisory Committee. Not later than 90 days after receiving a referral, the Pediatric Advisory Committee shall review the available information on the safe and effective use of the drug in the pediatric population, including study reports submitted under this section, and make a recommendation to the Commissioner as to appropriate labeling changes, if any. Not later than 30 days after receiving a recommendation from the Pediatric Advisory Committee, the Commissioner shall consider the recommendation and, if appropriate, make a request to the holders of approved applications for the drug to make any labeling change that the Commissioner determines to be appropriate. If a holder of an approved application for a drug, within 30 days after receiving a request to make a labeling change, does not agree to make a requested labeling change, the Commissioner may deem the drug to be misbranded under FFDCA. [FDAAA 502(b); PHSA 409I(c); 42 USC 284m]	
	Nothing in this subsection limits the authority of the United States to bring an enforcement action under the Federal Food, Drug, and Cosmetic Act [21 USC 301 et seq.] when a drug lacks appropriate pediatric labeling. Neither course of action (the Pediatric Advisory Committee process or an enforcement action referred to in the preceding sentence) shall preclude, delay, or serve as the basis to stay the other course of action. [FDAAA 502(b); PHSA 409I(c)(11); 42 USC 284m]	
Recommendation for Formulation Changes	If a pediatric study completed under public contract indicates that a formulation change is necessary and the Secretary agrees, the Secretary shall send a nonbinding letter of recommendation regarding that change to each holder of an approved application.	The FDAAA-amended PHSA 409I(c) does not include this provision, which had been PHSA 409I(c)(12).
Dissemination of Pediatric Information	No provision.	Requires that the Secretary, acting through the NIH Director and within one year of enactment, study and report to Congress on the feasibility of establishing a compilation of information on pediatric drug use. [FDAAA 502(b); PHSA 409I(d); 42 USC 284m]
Authorization of Appropriations	There are authorized to be appropriated to carry out this section $200 million for the first year; and such sums as are necessary for each of the succeeding fiscal years. Any amount appropriated shall remain available to carry out this section until expended. [FDAAA 502(b); PHSA 409I(e)(1); 42 USC 284m]	
	FY2002 was specified as the first year and reference was made to five succeeding years.	FY2008 is specified as the first year and the section refers to four succeeding years. [FDAAA 502(b); PHSA 409I(e)(1); 42 USC 284m]

Topic	Previous Law	FDAAA Title V, Sections 502(b-f) and 503
Foundation for the National Institutes of Health (FNIH)	The law continues to require the Secretary, acting through the Director of NIH, to establish a nonprofit corporation to be known as the Foundation for the NIH, which shall not be an agency or instrumentality of the U.S. Government. FNIH is to support the NIH in its mission (*including collection of funds for pediatric pharmacologic research*), and to advance collaboration with biomedical researchers from universities, industry, and nonprofit organizations. FNIH may solicit and accept gifts, grants, and other donations, establish accounts, and invest and expend funds in support of various education and research programs, including a program to collect funds for certain pediatric pharmacologic research and studies. The law includes requirements regarding a board of directors, corporate and financial organization and reporting, service of federal employees, intellectual property rights, dissemination of scientific results by grantees and FNIH. FNIH may transfer funds to the NIH and any funds transferred under this paragraph shall be subject to all federal limitations relating to federally-funded research. The law authorizes to be appropriated for FNIH an aggregate $500,000 for each fiscal year. [PHSA 499(c)(1)(C); 42 USC 290b(c)(1)(C)]	
	The FNIH provision related to drugs that the Secretary had referred for listing as needing pediatric studies. These included drugs with an approved or submitted application under FFDCA 505(j) [generic drugs], drugs *without* patent protection or marketing exclusivity, or drugs *with* patent protection whose sponsors declined the Secretary's requests for study. FNIH was to issue a proposal to award a grant to conduct such studies unless FNIH certified to the Secretary that FNIH did not have available funds, in which case the Secretary was required to refer the drug for inclusion on the list established under PHSA 409I. [PHSA 499(c)(1)(C) referred to PHSA 409I(a)(1)(A) and FFDCA 505A(d)(4)(C), each of which FDAAA has amended as well.]	Regarding a drug with an *unexpired patent* for which the Secretary requested pediatric pharmacologic research and studies that the sponsor declined, the Secretary must *first* determine whether FNIH has sufficient funds to initiate and fund in its entirety. If there are sufficient funds, the Secretary must *then* refer the study to the FNIH. If there are insufficient funds, the Secretary must consider whether to require the pediatric assessments under FFDCA 505B(b) (PREA). [FDAAA 502(c); PHSA 499(c)(1)(C); 42 USC 290b(c)(1)(C)]

Topic	Previous Law	FDAAA Title V, Sections 502(b-f) and 503
Advisory Committee on Pediatric Pharmacology	The law continues to require that the Secretary convene and consult an advisory committee on pediatric pharmacology. It specifies the committee composition, and requires that the committee advise and make recommendations to the Secretary, through the Commissioner and in consultation with the NIH Director, on matters relating to pediatric pharmacology. Specifies that the matters include pediatric research; identification of research priorities related to pediatric pharmacology and the need for additional treatments of specific pediatric diseases or conditions; and the ethics, design, and analysis of clinical trials related to pediatric pharmacology. [Section 14 of the Best Pharmaceuticals for Children Act; 42 USC 284m note]	
		FDAAA extends the advisory committee for another five years. [FDAAA 502(d); Section 14 of the Best Pharmaceuticals for Children Act; 42 USC 284m note]
Pediatric Subcommittee of the Oncologic Drugs Advisory Committee	The law continues the Pediatric Subcommittee of the Oncologic Drugs Advisory Committee. [Section 15 of the Best Pharmaceuticals for Children Act; 42 USC 284m note]	
		FDAAA requires that the Subcommittee provide recommendations to the internal review committee created under FFDCA 505B(f) regarding implementation of the Pediatric Research Equity Amendments and the Best Pharmaceuticals for Children amendments to FFDCA sections 505A and 505B with respect to the treatment of pediatric cancers. FDAAA also extends operations of the subcommittee for five years; and updates, to January 31, 2009, the requirement for the Secretary's report to congressional committees on patient access to new therapeutic agents for pediatric cancer, including access to single patient use of new therapeutic agents. [FDAAA 502(e); Section 15 of the Best Pharmaceuticals for Children Act; 42 USC 284m note]
Toll-Free Number for Consumer Reports of Adverse Events	This provision is not in previous law; it refers to a proposed rule (69 FR 21778, April 22, 2004).	Requires that the rule proposed by the Commissioner on April 22, 2004, take effect on January 1, 2008, unless the Commissioner issues the final rule before that date. Excluded from the rule's application are a drug approved under FFDCA Section 505, a nonprescription drug, and a drug whose packaging includes a toll-free number with which to report adverse events to the manufacturer or distributor. [FDAAA 502(f)]

Topic	Previous Law	FDAAA Title V, Sections 502(b-f) and 503
Investment in Tomorrow's Pediatric Researchers	In order to ensure the future supply of researchers dedicated to the care and research needs of children, the Director of the Institute, after consultation with the Administrator of the Health Resources and Services Administration, shall support activities to provide for: an increase in the number and size of institutional training grants to institutions supporting pediatric training; and an increase in the number of career development awards for health professionals who intend to build careers in pediatric basic and clinical research. [PHSA 452G(2); 42 USC 285g-10(a)(2)]	
		FDAAA inserts "..., including pediatric pharmacological research." [FDAAA 503(a); PHSA 452G(2); 42 USC 285g-10(a)(2)]
	The law authorized to be appropriated such sums as may be necessary for each of FY2001 through FY2005.	FDAAA does not have an authorization of appropriations provision for this subsection.
Loan Repayment for Pediatric Research	The law authorizes the Secretary, in consultation with the Director of NIH, to establish a pediatric research loan repayment program. Through such program, the Secretary shall enter into contracts with qualified health professionals who agree to conduct pediatric research, in exchange for the Federal Government repayment of certain principal and interest of the educational loans of such professionals. The law also addresses reimbursements for tax liability; and the application of other loan repayment provisions. [PHSA 487F(a)(1); 42 USC 288-6(a)(1)]	
		FDAAA inserts after "pediatric research": "including pediatric pharmacological research." [FDAAA 503(b); PHSA 487F(a)(1); 42 USC 288-6(a)(1)]

Title VI. Reagan-Udall Foundation

The Reagan-Udall Foundation for the FDA

Title VI of FDAAA adds new FFDCA Sections 770, 771, and 772 requiring the establishment of the Reagan-Udall Foundation for the Food and Drug Administration (the Foundation), a nonprofit corporation to advance FDA's mission regarding product development, innovation, and safety. The initial Board of Directors (the Commissioner, and the directors of NIH, CDC, and AHRQ) is to select the appointed members from a National Academy of Sciences-provided candidate list and then resign from the board. The ongoing board is to include representatives from industry, academic research organizations, government agencies, patient or consumer advocacy organizations, and health care providers.

FDAAA directs the Foundation to establish goals and priorities relating to unmet needs and then coordinate with federal programs, and award grants, contracts, and other agreements with public and private individuals and entities to advance those goals. Title VI directs the Commissioner to transfer between $500,000 and $1,250,000 to the Foundation from FDA appropriations each year.

Office of the Chief Scientist

FDAAA added a new FFDCA Section 910 that requires the Secretary to establish an Office of the Chief Scientist within the FDA Office of the Commissioner. Among the duties of the Secretary-appointed Chief Scientist would be to oversee, coordinate, and ensure quality and regulatory focus of FDA's intramural research programs.

Critical Path Public-Private Partnerships

A new FFDCA Section 566 authorizes the Secretary, through the Commissioner, to enter into collaborative agreements (Critical Path Public-Private Partnerships) with eligible educational or tax-exempt organizations to implement the FDA Critical Path Initiative. The agreements are to develop innovative, collaborative projects in research, education, and outreach for the purpose of fostering medical product innovation, enabling the acceleration of medical product development, and enhancing medical product safety.

The provision specifies the expertise and experience required of a partner entity. It requires the Secretary to submit an annual report to the authorizing congressional committees, and authorizes to be appropriated $5 million for FY2008 and such sums as may be necessary for each of FY2009 through FY2012.

Table 9. Law Created by *Reagan-Udall Foundation (FDAAA Title VI)*

Topic	FDAAA Title VI
Reagan-Udall Foundation for the FDA	FDAAA establishes a nonprofit corporation to be known as the Reagan-Udall Foundation for the Food and Drug Administration (The Foundation), to advance the mission of the FDA to modernize medical, veterinary, food, food ingredient, and cosmetic product development, accelerate innovation, and enhance product safety. The law lists the duties of the Foundation, criteria for formation, conduct duties, terms and administrative powers of the Board of Directors, and the Executive Director. The duties of the Foundation are to include "taking into consideration the Critical Path reports and priorities published by the Food and Drug Administration, identify unmet needs in the development, manufacture, and evaluation of the safety and effectiveness, including postapproval, of devices, including diagnostics, biologics, and drugs, and the safety of food, food ingredients, and cosmetics, including the incorporation of more sensitive and predictive tools and devices to measure safety." The law stipulates the roles of federal employees involved in the Foundation's functions. The *ex officio* members of the Board shall serve as incorporators and shall take whatever actions necessary to incorporate the Foundation. The Foundation shall be considered a corporation under Section 501(c) of the Internal Revenue Code of 1986, and shall be subject to the provisions of such section. The Executive Director may solicit and accept on behalf of the Foundation, any funds, gifts, grants, devises, or bequests of real or personal property, including from private entities, for the purposes of carrying out the duties of the Foundation. The Executive Director shall ensure that the funds received from the U.S. Treasury are held in separate accounts from funds received from other sources. To carry out certain provisions in this subtitle, from amounts appropriated to the FDA for each fiscal year, the Commissioner shall transfer to the Foundation not less than $500,000 and not more than $1,250,000. Recipients of grants, contracts, fellowships, memoranda of understanding, or cooperative agreements from the Foundation shall report to the Foundation regarding their activities on an annual basis. Beginning with FY2009, the Executive Director shall submit to Congress and the Commissioner an annual report on the Foundation's activities. [FDAAA 601; FFDCA 770; 21 USC 379dd]
	The Foundation shall, if practicable, be located not more than 20 miles from the District of Columbia. [FDAAA 601; FFDCA 771; 21 USC 379dd-1]
	The Commissioner shall receive and assess the required annual reports concerning the Foundation; and, beginning with FY2009, submit to Congress an annual report summarizing the information provided by the Foundation, and other required information. The provisions of this subchapter shall have no effect on any grant, contract, memorandum of understanding, or cooperative agreement between the FDA and any other entity entered into before, on, or after the date of enactment. 742(b) of the FFDCA (21 USC 379l(b)) is amended by adding at the end the following: "Any such fellowships and training programs under this section or under Section 770(d)(2)(A)(ix) may include provision by such scientists and physicians of services on a voluntary and uncompensated basis, as the Secretary determines appropriate. Such scientists and physicians shall be subject to all legal and ethical requirements otherwise applicable to officers or employees of the Department of Health and Human Services." [FDAAA 601; FFDCA 772; 21 USC 379dd-2]

Topic	FDAAA Title VI
Office of the Chief Scientist	A new section in FFDCA requires the Secretary to create an Office of the Chief Scientist within FDA's Office of the Commissioner. (Duties specified). [FDAAA 602; FFDCA 910; 21 USC 399a]
Critical Path Public-Private Partnerships	FDAAA authorizes the Secretary, acting through the Commissioner, to enter into collaborative agreements (Critical Path Public-Private Partnerships) with educational or tax-exempt organizations to implement the FDA Critical Path Initiative by developing innovative, collaborative projects in research, education, and outreach for the purpose of fostering medical product innovation, enabling the acceleration of medical product development, and enhancing medical product safety; and authorizes to be appropriated $5 million for FY2008 and such sums as may be necessary for each of FY2009 through FY2012. [FDAAA 603; FFDCA 566; 21 USC 360bbb-5]

Title VII. Conflicts of Interest

Title VII of FDAAA, *Conflicts of Interest*, contains provisions that revise FDA's approach to advisory committee members' conflicts of interest. FDA uses advisory committees to provide the agency with independent advice from outside experts on issues related to human and veterinary drugs, biological products, medical devices, and food. Advisory committees make recommendations to FDA, which FDA may or may not follow. To be credible and useful, many say that FDA must eliminate or reduce conflicts of interest in its committees. However, others note that the most expert members in the field are often those involved directly or indirectly in the activities about which FDA is seeking advice, creating the potential for such conflicts. In 2006 and 2007, the media reported that FDA advisory committees are biased in favor of drug approval, and that many committee members have conflicts of interest.[21]

For further information, see CRS Report RS22691, *FDA Advisory Committee Conflict of Interest*, by Erin D. Williams.

Prior to the passage of FDAAA, the law generally required that committee members be free from conflicts of interest, but allowed for exceptions to that rule under specific circumstances. A conflict of interest might have required a potential committee member to disclose the conflict, refrain from voting, and/or not participate in a committee, depending on the nature of the conflict. The law was articulated primarily in three locations: (1) the Federal Advisory Committee Act (5 USC Appendix; FACA); (2) the FDA advisory committee policy (21 USC 355(n)), which applied only to trials of drugs and biologics — not devices; and (3) a law governing special government employees — such as advisory committee members — Acts Affecting Personal Financial Interest (18 USC 208).

FDAAA inserts a new provision into Chapter VII, Subchapter A, of the FFDCA, effective October 1, 2007. The provision changes both the process of recruiting advisory committee members, as well as some circumstances under which and processes by which conflict-of-interest waivers may be granted. The new provisions repeal 21USC 355(n), but move much of its substance to a new location; the effect is that the requirements previously only applicable to drug and biologic advisory committees apply to committees providing advice on all types of products that FDA regulates.

FDAAA defines an advisory committee as a FACA-covered entity that provides the Secretary with advice and recommendations regarding activities of the FDA, and defines financial interest as defined under 18 USC 208(a). This definition covers activities such as a person's or their family members' current or future employment, trusteeship, or directorship. On its face, it does not apply to activities such as stock

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[21] See, for example, Shankar Vedantam, "Group Says FDA, Advisory Panels Show Bias Toward Drug Approvals," *Washington Post*, August 9, 2006, available online at [http://www.washingtonpost.com/wp-dyn/content/article/2006/08/28/AR2006082800984.html].

ownership, former employment, or receipt of a grant or contract, although FDA's regulations do require disclosure of these types of activities.

FDAAA requires advisory committee member recruitment mechanisms to be focused on reaching experts from areas such as academia, medical research institutions, and public interest and consumer groups. It also discourages the number of permissible exceptions to the financial conflict rules, such as the use of waivers or written certifications.

FDAAA requires advisory committee members' full financial disclosure prior to a meeting on a related matter. It precludes participation by a member with a conflict of interest unless exempted by the Office of Government Ethics. The Act also allows a waiver of the voting restriction if necessary to provide the committee with essential expertise.

FDAAA restricts the percentage of committees' membership that may consist of people who have received one of three types of exceptions to the financial conflict prohibitions: (1) waivers granted by the Secretary under newly created FDAAA provisions, (2) written determinations under 18 USC 208(b)(1), and (3) written certifications under 208(b)(3). The Secretary is required to determine the number and proportion of advisory members who received exceptions in FY2007. For FY2008 through FY2012, the Secretary must reduce the proportion of excepted members by an additional 5% per year from the FY2007 number. This limitation does not apply to financial interest exemptions made under 18 USC 208(b)(2).

FDAAA requires public disclosures for conflict-of-interest determinations, certifications, and waivers (but not 208(b)(2) exemptions), except for those exempted from disclosure under the Freedom of Information Act of 1974 (5 USC 522). It requires the Secretary to submit annual reports regarding advisory committee membership and conflict-of-interest waivers. It also requires the Secretary to review and update FDA conflict-of-interest guidance not less than once every five years.

Table 10. Comparison of *Conflicts of Interest (FDAAA Title VII)* with Previous Law

Topic	Previous Law	FDAAA Title VII
Advisory Committee	FDA advisory committee policy applied only to drug and biologic advisory committees. [21 USC 355(n)]	FDA policy applies to all Federal Advisory Committee Act (FACA) committees that provides advice or recommendations to the Secretary regarding the FDA. [FDAAA 701(a); FFDCA 712(a)(1); 21 USC 371 et seq.]
Financial Interest	[A committee member who] participates personally and substantially as a government officer or employee, through decision, approval, disapproval, recommendation, the rendering of advice, investigation, or otherwise, in a judicial or other proceeding, application, request for a ruling or other determination, contract, claim, controversy, charge, accusation, arrest, or other particular matter in which, to his knowledge, he, his spouse, minor child, general partner, organization in which he is serving as officer, director, trustee, general partner or employee, or any person or organization with whom he is negotiating or has any arrangement concerning prospective employment, has a financial interest. (Defined in 18 USC 208(a)) [Notes: The scope of disqualifying financial interests under 18 USC 208(a) have been interpreted to include any potential for gain or loss to the employee, which would include interests such as stock ownership according to 5 C.F.R. 2640.103(b). Exemptions and waivers in 18 USC 208(b) apply. Penalties in 18 USC 216 apply.] [FDAAA 701(a); FFDCA 712(a)(2); 21 USC 371 et seq.]	
Recruitment	The Commissioner is required to publish one or more notices in the Federal Register each year requesting nominations for voting members. [21 CFR 14.82]	
		In addition to publications in the Federal Register, the Secretary is required to develop and implement strategies on effective outreach to potential members of advisory committees at universities, colleges, other academic research centers, professional and medical societies, and patient and consumer groups. The Secretary shall seek input from professional medical and scientific societies to determine the most effective informational and recruitment activities. The Secretary shall also take into account the advisory committees with the greatest number of vacancies. [FDAAA 701(a); FFDCA 712(b)(1); 21 USC 371 et seq.]
Evaluation and Criteria	No provision.	When considering a term appointment to an advisory committee, the Secretary shall review the expertise of the individual and the financial disclosure report filed by the individual pursuant to the Ethics in Government Act of 1978 for each individual under consideration for the appointment, so as to reduce the likelihood that an appointed individual will later require an exemption or waiver under 18 USC 208(b). [FDAAA 701(a); FFDCA 712(b)(2); 21 USC 371 et seq.]

Topic	Previous Law	FDAAA Title VII
Disclosure of Financial Interests	Each member of a drug or biologic advisory committee had to publicly disclose all conflicts of interest that he or she may have with the work to be undertaken by the panel. [21 U.S.C. 355(n)]	Prior to a meeting of an advisory committee, each member of the committee shall disclose to the Secretary financial interests in accordance with subsection 18 USC 208(b). [FDAAA 701(a); FFDCA 712(c)(1); 21 USC 371 et seq.]
Prohibitions In General	18 USC 208, which remains in effect, allows criminal penalties to be imposed on any person participating in an advisory committee who has conflicts based on certain financial interests, such as current or future employment, or on a directorship role in an organization. The scope of these disqualifying financial interests has been interpreted broadly in regulation to include any potential for gain or loss to the employee. [5 C.F.R. 2640.103(b)]	
		An advisory committee member may not participate with respect to any matter considered by the advisory committee if such member (or an immediate family member of such member) has a financial interest that could be affected by the advice given to the Secretary with respect to such matter, excluding interests exempted in regulations issued by the Director of the Office of Government Ethics as too remote or inconsequential to affect the integrity of the services of the government officers or employees to which such regulations apply. [FDAAA 701(a); FFDCA 712(c)(2)(A); 21 USC 371 et seq.]
Waivers and Exemptions	21 USC 208(b), which remains in effect, provides for four exceptions to the general prohibition on acts affecting a personal financial interest: (1) a written determination that the interest is not substantial, (2) an exemption because the interest is too remote, (3) a certification that the need for the individual's services outweighs the potential for a conflict, and (4) certain exemptions if the conflict relates to one's Indian or Native Alaskan status.	
	A committee may confer with any person who may have information or views relevant to any matter pending before the committee. [21 CFR 14.31(a)]	The Secretary may grant a waiver of the FDAAA-created prohibition to allow a non-voting or voting member to participate if such waiver is necessary to afford the advisory committee essential expertise. [FDAAA 701(a); FFDCA 712(c)(2)(B); 21 USC 371 et seq.]

Topic	Previous Law	FDAAA Title VII
Waiver Limitations	No provision.	Limitations are placed on three types of exceptions to the financial conflict prohibitions: (1) waivers granted by the Secretary under newly created FDAAA provisions, (2) written determinations under 18 USC 208(b), and (3) written certifications under 208(b)(3). For FY2007, the Secretary is required to determine the number and proportion of advisory members who received exceptions, and limit the total number of exceptions to the following proportions of the FY2007 number: 95% for FY2008, 90% for FY2009, 85% for FY2010, 80% for FY2011, and 75% for FY2012. [FDAAA 701(a); FFDCA 712(c)(2)(C); 21 USC 371 et seq.]
Disclosure of Waiver	No provision.	For waivers granted under the terms of FDAAA or under 18 USC 208(b)(1) or (3), the Secretary is to disclose on the FDA website the type, nature, and magnitude of the pertinent financial interests and the reasons for the Secretary's action. The disclosure should not include information that is not subject to a Freedom of Information Act request. The Secretary is required to make the disclosure not less than 15 days prior to an advisory committee meeting, or, in the event that the financial interests became known to the Secretary less than 30 days prior to the meeting, no later than the date of the meeting. Disclosures are to be included in the public record and transcript of each meeting. [FDAAA 701(a); FFDCA 712(c)(3),(d); 21 USC 371 et seq.]
Annual Report	No provision.	The Secretary is to submit annual reports to relevant congressional committees describing advisory committee vacancies, nominees, and the number of nominees willing to serve; the number of conflict-related disclosures per meeting and the percentage of members who did not require such disclosures; the number of times required disclosures occurred less than 30 days in advance of meetings; and how the Secretary plans to reduce the number of vacancies on advisory committees and increase the number of nominations, including those of academicians or practitioners. [FDAAA 701(a); FFDCA 712(e); 21 USC 371 et seq.]
Guidance Review		The Secretary is to review and update FDA conflict of interest guidance not less than once every five years. [FDAAA 701(a); FFDCA 712(f); 21 USC 371 et seq.]

Topic	Previous Law	FDAAA Title VII
Conforming Amendment	21 USC 355(n) applied conflicts provisions only to committees focused on drugs and biologics.	Provisions that were in 21 USC 355(n) are moved to FFDCA Title VII, subchapter A [21 USC 371], as modified, so that they apply to all FDA FACA advisory committees. [FDAAA 701(b); FFDCA 505(n); 21 USC 355(n)]
Effective Date	No provision.	October 1, 2007. [FDAAA 701(a); 21 USC 355 note]

Title VIII. Clinical Trial Databases

Title VIII of FDAAA, *Clinical Trial Databases*, expands requirements for the registration of clinical trials, and adds requirements for the publication of their results. The text of the title was arrived at after extensive discussions, which required an understanding of the nature of scientific inquiry and medical product development.

Scientific inquiry is, at its best, an objective exercise in which results are not pre-ordained, and all valid findings are published. Medical product development depends upon traditional scientific methods, and product sponsors are typically business enterprises. Prior to marketing, product sponsors are required to demonstrate the safety and effectiveness of their products, typically through clinical trials. However, both sponsors and medical journals may be reluctant to publish the results of trials that fail to show that products perform better than a placebo, or that raise too many safety concerns. In 2004, Congress and others raised questions about the safety and effectiveness of several FDA-approved products (e.g., antidepressants, anti-inflammatory drugs, and cardiac stents) about which unfavorable trial results had not been publicly disclosed.[22] The issue of public access to all trial results, regardless of their findings, then gained significant traction.

For further information, see CRS Report RL32832, *Clinical Trials Reporting and Publication*, by Erin D. Williams.

Prior to the enactment of FDAAA, clinical trial registration was required at the outset of certain clinical trials testing drugs to treat life-threatening diseases or conditions. This requirement was criticized because it did not mandate the registration of a broader range of trials, because it contained no enforcement mechanism, and because it did not require the posting of trial results. Title VIII of FDAAA contains provisions related to all three criticisms.

FDAAA's provisions apply to trials involving not only drugs, but also devices and biologics. The Act includes requirements pertaining to most clinical trials beyond Phase I. In general, FDAAA requires that specified information be submitted by the trial's responsible party (RP; usually the trial sponsor), to the NIH Director. Following submission, the NIH Director is to make the information publicly available via the Internet, with specified exceptions. Enforcement mechanisms are provided for noncompliant RPs. For the purpose of carrying out the clinical trials database provisions, FDAAA authorizes $10,000,000 for each fiscal year. Further details of the way that FDAAA amends current law are discussed below, in subsections entitled Registry; Results; Coordination, Compliance, and Enforcement; and Other Items.

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[22] Shankar Vedantam, "Antidepressant Makers Withhold Data on Children," *Washington Post*, January 29, 2004, p. A1; and Catherine De Angelis et al., "Clinical Trial Registration: A Statement from the International Committee of Medical Journal Editors," *New England Journal of Medicine*, vol. 351, no. 12, September 16, 2004, p. 1250.

Registry

FDAAA requires the expansion of the existing data bank (clinicaltrials.gov, which is hosted by the National Library of Medicine) to include the registration of applicable drug, device, and biologics trials as described above. Submissions for the registry are to include four types of material: descriptive information about the trial, recruitment information for potential subjects, trial location and contact information, and administrative data, such as protocol identification numbers. The information required by FDAAA includes and expands upon that required under previous law, as well as elements of the World Health Organization's International Clinical Trials Registry Platform registration data set.[23] The Secretary may modify these requirements by regulation.

In making the information public, the NIH Director is to ensure that it is searchable in a number of specified ways. The Director is also to ensure that the registry is easily used by the public, and that entries may be easily compared.

FDAAA generally requires the RP to submit information to the NIH Director within 21 days after the first patient is enrolled in the trial. This requirement is similar to the one that existed previously. The NIH Director is required to post information about drug and biologics trials not later than 30 days after the information is submitted by the RP. In contrast, for device trials, information is to be posted not earlier than the date of FDA approval or clearance, and not later than 30 days after approval or clearance.

The RP for an applicable clinical trial is required to submit updates to the NIH Director to reflect changes to registry information. The Director is to make the update information publicly available and generally ensure that previously submitted information remains accessible.

Results

Previous law allowed for the inclusion of results information with the consent of the trial sponsor, but did not require it. FDAAA requires the Secretary, acting through the NIH Director, to expand the registry to include results of applicable clinical trials and to ensure that the results are made publicly available via the Internet. Three categories of results information are to be added according to the following timeframe. First, beginning 90 days after FDAAA enactment, the Secretary is to ensure that the registry contains links to specified *existing results*. Second, within one year after FDAAA enactment, the Secretary, acting through the NIH Director, is to expand the registry to include specified *basic results*. Third, within three years after FDAAA enactment, the Secretary is to add information to create an *expanded registry and results* data bank by rulemaking.

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[23] "The World Health Organization announces new standards for registration of all human medical research," World Health Organization website, May 19, 2006, at [http://www.who.int/mediacentre/news/releases/2006/pr25/en/index.html].

The first type of results to be made available in the registry, *existing results*, consists of links to existing FDA and NIH documentation. These results must be posted for clinical trials that form the primary basis of an efficacy claim or are conducted after product approval or clearance. Links to this information are to be posted not earlier than 30 days after the approval or clearance of the product, or not later than 30 days after the information becomes publicly available.

The second type of results to be made available in the registry, *basic results*, consists of demographic, outcome, and scientific point of contact information, as well as agreements that restrict the principal investigator (PI) to publicly discuss or publish results. These results must be submitted for products that FDA has approved, licensed, or cleared. The RP is to submit basic results information to the Secretary within one year following the earlier of the estimated or actual completion date of the trial, with certain exceptions.

The third type of results information, *expanded registry and results*, is to be submitted to and made available in the registry pursuant to rulemaking. Rulemaking is to occur within three years of FDAAA enactment. Rulemaking is to require the submission of clinical trial information for approved or cleared products, and is to determine whether results information for unapproved products should be included as well. The expanded registry and results database is to include basic results, as well as: (1) a non-technical summary of results; (2) a technical summary of results; (3) protocol information; and (4) such other categories the Secretary determines are appropriate.

FDAAA directs the Secretary to promulgate a second set of regulations regarding adverse event reporting. Not later than 18 months after FDAAA enactment, the Secretary is to determine the best method for including appropriate information on serious and frequent adverse events in the registry and results database. If the Secretary fails to take action within 24 months after FDAAA enactment, the Secretary must include specified adverse-event related elements in the registry and results database. FDAAA's adverse event reporting requirements are limited to drugs and biologics. The House passed a measure that would expand it to devices as well.[24]

An RP may voluntarily submit information about trials that are not required for submission if the RP has made submissions for all required trials. If necessary to protect public health, the Secretary may require the submission of additional registry and results information.

Coordination, Compliance, and Enforcement

The former registry law did not contain any specific compliance or enforcement measures. By contrast, FDAAA contains four sets of enforcement and compliance requirements, and specifies civil penalties for noncompliance. One set attaches to federal grant funding. A second set of compliance requirements must be met when submitting a drug, biological product, or device submission to the FDA. A third set

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[24] H.Cong.Res. 217.

of FDAAA requirements specifies that clinical trial information submitted by the RP must be truthful and not misleading in any particular. Under a fourth set of requirements, the NIH Director is to include a notification in the database if an RP fails to submit required clinical trials registry or results information.

Previous law did not specify penalties or enforcement mechanisms related to registry requirements. Previous law contained general mechanisms for enforcing compliance with FDA requirements that may have been applicable, but which FDA never used for registry requirement violations. FDAAA amends the *prohibited acts* section of the FFDCA, to clarify that the clinical trial databases provisions are enforceable. FDAAA also amends the FFDCA's *civil monetary penalty* provisions, articulating those for noncompliance with the clinical trial database requirements.

Other Items

FDAAA contains a few additional provisions pertaining to informed consent, state clinical trial databases, and FFDCA violations. It requires the Secretary to update investigational new drug regulations so that informed consent includes a statement that clinical trial information has been or will be submitted for inclusion in the registry databank. Previous law contained informed consent requirements, but none specific to the registry.

The Act prohibits any state or political subdivision from requiring the registration of clinical trials or their results in a database. It also specifies that the fact of submission of off-label use clinical trial information, if in compliance with revised registry and results database requirements, is not to be construed as evidence of a new intended use. In addition, the availability of compliant database submissions is not to be considered as labeling, adulteration, or misbranding under the FFDCA.

Table 11. Comparison of *Clinical Trial Databases (FDAAA Title VIII)* with Previous Law

Topic	Previous Law	FDAAA Title VIII
Types of Trials	Requirements applied to drug trials only.	Requirements apply to applicable trials of drugs, devices, and biologics. [FDAAA 801(a)(2); PHSA 402(j)(1)(A)(i)-(iii); 42 USC 282(j)]
Applicable Drug and Biologic Trials (trials for which registration and, in some cases, results reporting is required)	Applicable drug trials are: (1) investigational new drug trials (whether federally or privately funded) of experimental treatments for serious or life-threatening diseases and conditions under regulations promulgated pursuant to section 21 USC 355(i) [re: investigational new drugs]; or (2) treatment use of investigational new drugs: information pertaining to experimental treatments for serious or life-threatening diseases and conditions that may be available - (i) under a treatment investigational new drug application that has been submitted to the Secretary under 21 USC 360bbb(c); or (ii) as a Group C cancer drug (as defined by the National Cancer Institute). Trials of biologics are not applicable.	Applicable drug and biologics trials are controlled clinical investigations, other than Phase I clinical investigations, of a drug subject to FFDCA 505 or PHSA 351. [FDAAA 801(a)(2); PHSA 402(j)(1)(A)(iii); 42 USC 282(j)] [*Clinical investigations* is defined as in 21 CFR 312.3 or successor regulations: any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. For the purposes of this part, an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice. *Phase I* is defined as in 21 CFR 312.21or any successor regulation: the initial introduction of an investigational new drug into humans. Phase 1 studies are typically closely monitored and may be conducted in patients or normal volunteer subjects.]
Applicable Device Trials (trials for which registration and, in some cases, results reporting is required)	None.	Applicable device trials are prospective clinical studies of health outcomes comparing an intervention with a device subject to FFDCA 510(k) [re device clearance], 515 [re: premarket approval of devices], or 520(m) [re: humanitarian devices] against a control in human subjects (other than a small clinical trial to determine the feasibility of a device, or a clinical trial to test prototype devices where the primary outcome measure relates to feasibility and not to health outcomes); and pediatric postmarket surveillance as required under FFDCA 522 [as amended by the PMDSIA provisions of FDAAA]. [FDAAA 801(a)(2); PHSA 402(j)(1)(A)(ii); 42 USC 282(j)]

Topic	Previous Law	FDAAA Title VIII
Responsible Party (RP; the person required to submit information)	The sponsor is to submit required information.	The RP is the sponsor, as defined by 21 CFR 50.3 [a person who initiates a clinical investigation, but who does not actually conduct the investigation...]. The RP may be the PI if designated by sponsor, grantee, contractor, or awardee, so long as the PI is responsible for conducting the trial, has access to and control over data, has the right to publish trial results, and has the authority to meet the RP responsibilities. [FDAAA 801(a)(2); PHSA 402(j)(1)(A)(ix); 42 USC 282(j)]
Who Receives the Information	Required information is to be submitted to the NIH Director. [FDAAA 801(a)(2); PHSA 402(j)(2)(C),(D)(iv); 42 USC 282(j)]	
Public Access	The Secretary is to disseminate via information systems, which were to include toll-free telephone communications	The NIH Director shall ensure clinical trial information is made publicly available through the Internet, and in a manner easily used by the public and with entries that are easily compared. [FDAAA 801(a)(2); PHSA 402(j)(2)(A)(i),(3)(B)(ii),(G); 42 USC 282(j)]
Content of Registry Submission	Submissions are to include the trial purpose, eligibility criteria, location(s) of trial, enrollment point of contact, description of whether and how the manufacturer or sponsor will respond to requests for protocol exception, with appropriate safeguards, for single-patient and expanded protocol use of the new drug, particularly in children. With sponsor consent, submissions may include the results of trials, potential toxicities, or adverse effects.	The registry submission is to include: (1) descriptive information (title, summary, purpose, outcome measures, etc.); (2) recruitment information (eligibility criteria, gender, age limits, etc.); (3) location and contact information (sponsor name, RP, facility information, etc.); and (4) administrative data (protocol identification numbers, FDA IND/IDE protocol number, etc.). (Note: FDAAA submission requirements are worded differently than under previous law, but include all elements that were required under previous law.) [FDAAA 801(a)(2); PHSA 402(j)(2)(A)(ii); 42 USC 282(j)] The Secretary may modify these requirements by regulation, if the Secretary provides a rationale as to why the modification improves and does not reduce the information. [FDAAA 801(a)(2); PHSA 402(j)(2)(A)(iii); 42 USC 282(j)] Note: the Secretary is not required to post information otherwise protected under 5 USC 552. [FDAAA 801(a)(2); PHSA 402(j)(6); 42 USC 282(j)]
Registry Searchable Categories	Not specified.	The NIH Director is to ensure that it is searchable by keyword, the disease or condition being studied, the name of the intervention, the location of the trial, the age group being studied, and the trial phase, sponsor, recruitment status, and identification number(s). An additional category is to be added within 18 months of FDAAA enactment — safety issue being studied as a primary or secondary outcome. The Director is to make the registry searchable by other elements that the Director deems necessary. [FDAAA 801(a)(2); PHSA 402(j)(2)(B)(i); 42 USC 282(j)]

Topic	Previous Law	FDAAA Title VIII
Timing of Submission to Registry	Required information is to be submitted not later than 21 days after the approval of the protocol.	For trials initiated or ongoing 90 days after FDAAA enactment, the RP is to submit required information not later than the later of: (1) 90 days after FDAAA enactment; (2) 21 days after the first patient is enrolled in the trial; or (3) for trials that are not for serious or life-threatening diseases or conditions that are ongoing as of the date of enactment, one year after the date of enactment. [FDAAA 801(a)(2); PHSA 402(j)(2)(C); 42 USC 282(j)]
Timing of Registry Posting	No provision.	The NIH Director is required to post information about drug and biologics trials not later than 30 days after the information is submitted by the RP. For device trials, information is to be posted not earlier than the date of clearance under FFDCA 510(k), or approval under FFDCA 515 or 520(m), and not later than 30 days after approval or clearance. Beginning one year after enactment, for devices previously cleared or approved, registry information is to be posted not later than 30 days after the date that clinical trial results information is required to be posted by the Secretary. [FDAAA 801(a)(2); PHSA 402(j)(2)(D); 42 USC 282(j)]
Glossary	No provision.	The Secretary, acting through the NIH Director, shall ensure that a glossary of technical terms is publicly posted. [FDAAA 801(a)(2); PHSA 402(j)(3)(B)(iii); 42 USC 282(j)]

Topic	Previous Law	FDAAA Title VIII
Content of Results Postings	With sponsor consent, the registry may include information about the results of included trials, including potential toxicities or adverse effects.	There are three different categories of results information: -*Existing results* include: (1) FDA Information (pertinent advisory committee documentation, FDA results assessments, FDA public health advisories, etc.); and (2) NIH Information (pertinent Medline citations and NLM product label entries). The Secretary may also provide links to the above types of results information for trials submitted to the data bank prior to FDAAA's enactment. [FDAAA 801(a)(2); PHSA 402(j)(3)(A)(ii); 42 USC 282(j)] -*Basic results* include: (1) demographic and baseline characteristics of the patient sample; (2) primary and secondary outcomes (which the NIH Director is to link to outcome measure information submitted with registration); (3) point of contact for scientific information and results; and (4) any agreements between the sponsor and PI that restrict the ability of the PI to publicly discuss or publish results in a scientific or academic journal. [FDAAA 801(a)(2); PHSA 402(j)(3)(C); 42 USC 282(j)] -*Expanded registry and results* include *basic results*, as well as: (1) a non-tecnhical summary of results; (2) a technical summary of results; (3) protocol information; (4) such other categories the Secretary determines are appropriate. [FDAAA 801(a)(2); PHSA 402(j)(3)(D)(iii); 42 USC 282(j)] -The Secretary is not required to post information otherwise protected under 5 USC 552. [FDAAA 801(a)(2); PHSA 402(j)(6); 42 USC 282(j)]
Risk Communication	No provision.	The Secretary, acting through the NIH Director, shall ensure that information created in consultation with risk communication experts is to be provided to help ensure that the specified basic results in the database do not mislead patients or the public. [FDAAA 801(a)(2); PHSA 402(j)(3)(B)(iii); 42 USC 282(j)]

Topic	Previous Law	FDAAA Title VIII
Trials For Which Results Are To Be Posted	Trials that have sponsor consent for posting of results.	-*Existing results* are to be posted for trials submitted after the enactment of FDAAA that form the primary basis of an efficacy claim or are conducted after the drug or biologics is approved or after the device is cleared or approved for which the specified information is publicly available. [FDAAA 801(a)(2); PHSA 402(j)(3)(A)(i); 42 USC 282(j)] -*Basic results* are to be posted for drugs that are approved under FFDCA 505, biologics licenced under PHSA 351, and devices cleared under 510(k) or approved under 515 or 520(m). [FDAAA 801(a)(2); PHSA 402(j)(3)(C); 42 USC 282(j)] -*Expanded registry and results* are to include information for each applicable clinical trial for drugs that are approved under FFDCA 505, biologics licenced under PHSA 351, and devices cleared under 510(k) or approved under 515 or 520(m). Rulemaking is to establish whether information shall also be required for applicable clinical trials for drugs not approved under FFDCA 505, biologics not licenced under PHSA 351, and devices not cleared under 510(k) or not approved under 515 or 520(m) (whether approval, licensure, or approval was sought). [FDAAA 801(a)(2); PHSA 402(j)(3)(D)(ii); 42 USC 282(j)] -*Additional submissions* may be made voluntarily if an RP has made submissions for all required trials. Additional submissions may also be required by the Secretary if necessary to protect the public health. [FDAAA 801(a)(2); PHSA 402(j)(4); 42 USC 282(j)]

Topic	Previous Law	FDAAA Title VIII
Timing of Results Submission	Not specified.	-*Existing results* information is publicly available and does not require submission by the RP. -*Basic results* are to be submitted not later than one year following the earlier of the estimated or actual completion date of the trial. This time period may be expanded to 18 months via *expanded registry or results*-related rulemaking. This time period may be delayed for up to two years with the submission of a certificate that approval of a new use is being sought. If a manufacturer makes such a certification, it must make equal certifications for all required trials for a given application. The Secretary may grant a waiver to results submission if extraordinary circumstances justify it, as long as it is consistent with public health or national security. The Secretary may grant an extension if the RP makes a written request demonstrating good cause. If an extension is granted, the Secretary must notify the NIH Director within 30 days. -*Expanded registry and results* are to be submitted pursuant to rulemaking according to the same timeline as *basic results*. [FDAAA 801(a)(2); PHSA 402(j)(3)(D)(iv); 42 USC 282(j)] -*If necessary to protect public health*, the Secretary may require the submission of registry and results for a specified clinical trial information within 30 days of notice to the RP. [FDAAA 801(a)(2); PHSA 402(j)(4)(B); 42 USC 282(j)]
Timing of Results Posting	Not specified.	-*Existing results* links are to be provided beginning not later than 90 days after FDAAA enactment, and not earlier than 30 days after the approval or clearance of the product, or not later than 30 days after the information becomes publicly available. [FDAAA 801(a)(2); PHSA 402(j)(3)(A)(i); 42 USC 282(j)] -*Basic results* are to be posted beginning not later than one year after FDAAA enactment and not later than 30 days after submission. -*Expanded registry and results* are to be posted not later than 30 days following submission, pursuant to rulemaking. [FDAAA 801(a)(2); PHSA 402(j)(3)(C),(D),(G); 42 USC 282(j)]

Topic	Previous Law	FDAAA Title VIII
Expanded Registry and Results Rulemaking	Not applicable.	In addition to the points specified above, required rulemaking regarding the expanded registry and results database is to: (1) determine whether the time period for submission of results should be increased from one year to 18 months; (2) specify whether and by when expanded information must be submitted regarding trials for which basic results submissions were made prior to the rule's enactment; (3) establish a standard submission format, additional information that is nontechnical and understandable to patients, and procedures for quality control; (4) specify the appropriate timing and requirements for updates of clinical trial information; (5) specify requirements for a statement accompanying voluntary submissions; and (6) specify additions or modifications to the manner of reporting the basic results information. In the rulemaking process the Secretary is to consider the World Health Organization data set, and is to hold a public meeting 18 months after FDAAA's enactment to provide an opportunity for public input regarding the rulemaking requirements. [FDAAA 801(a)(2); PHSA 402(j)(3)(D); 42 USC 282(j)]
Adverse Events	With sponsor consent, the registry may include information about the results of included trials, including potential toxicities or adverse effects.	Not later than 18 months after FDAAA enactment, the Secretary is to determine the best method for including appropriate information on serious and frequent adverse events in the registry and results database. If the Secretary fails to take action within 24 months after FDAAA enactment, the Secretary must, in consultation with risk communication experts, include the following elements in the registry and results database: (1) a table of serious adverse events (both anticipated and unanticipated) grouped by organ system, with number and frequency of such event in each arm of the trial; and (2) a similar table of other adverse events that exceed a frequency of five percent within any arm of the trial. Adverse event clinical trial information is deemed to be included in the registry and results database pursuant to the basic results requirements. (Note: FDAAA's adverse event reporting requirements are limited to drugs and biologics. The House passed a measure that would expand it to devices as well (H.Cong.Res 217).) [FDAAA 801(a)(2); PHSA 402(j)(3)(I); 42 USC 282(j)]

Topic	Previous Law	FDAAA Title VIII
Registry Updates	No provision.	The RP for an applicable clinical trial shall submit updates to the NIH Director to reflect changes to registry information. Updates shall: (1) be submitted not less than once every 12 months, unless there were no changes; (2) include the dates of any such changes; and (3) be submitted regarding changes in recruitment status or trial completion not later than 30 days after the change. The Director shall make update information publicly available, and, except with regard to recruitment status, individual site status, location, and contact information, ensure that previously submitted information remains accessible. [FDAAA 801(a)(2); PHSA 402(j)(4)(C); 42 USC 282(j)]
Coordination and Compliance: HHS Funded Trials	No provision.	For trials supported by grants from HHS agencies, any required grant or progress report forms must include a certification that the RP has made all required submissions to the registry and results database. The heads of the HHS agencies must verify that such information has been submitted before releasing funding. Grantees who have not made all required submissions are to be given notice and an opportunity to remedy their noncompliance. [FDAAA 801(a)(2); PHSA 402(j)(5)(A); 42 USC 282(j)]
Coordination and Compliance: Trials Funded by Federal Agencies Other Than HHS	No provision.	For research without HHS funding, but supported by grants from other federal agencies, the Secretary must consult with other agencies conducting research in accordance with any part of 45 CFR 46 (federal protections for human research subjects) and develop strategies comparable to the HHS protocol for ensuring required submissions are made. [FDAAA 801(a)(2); PHSA 402(j)(5)(A)(iv); 42 USC 282(j)]
FDA Application Certifications	No provision.	Applications for approval or clearance of drugs, devices, and biologics are to include a certification that the RP has made all required submissions to the registry and results database. Where available, such certification is to include the National Clinical Trial control numbers. FFDCA 505, 510, 515, and 520 (governing submissions for drug, biologic and device approval as well as device clearance and humanitarian device exemptions) are each amended to include the statement that "such application shall include the certification requirement under PHSA 402(j)(5)(B) (which shall not be considered an element of such application)." [FDAAA 801(a)(2); PHSA 402(j)(5)(B); 42 USC 282(j)]
Truthfulness of Submitted Information	No provision.	Clinical trial information submitted by the RP must be truthful and not misleading in any particular. [FDAAA 801(a)(2); PHSA 402(j)(5)(D); 42 USC 282(j)]

Topic	Previous Law	FDAAA Title VIII
Quality Control Pilot Project	No provision.	The Secretary must conduct a pilot project to determine the best method of quality control (QC) to ensure that submitted information is not false or misleading in any particular and is non-promotional. The pilot project shall continue until the effective date of the regulations for the expanded registry and results database. The regulations are to incorporate recommendations from the project. If the Secretary determines that clinical trial information was not submitted or did not meet QC standards as required, the Secretary must notify and give the RP an opportunity to remedy the noncompliance. [FDAAA 801(a)(2); PHSA 402(j)(5)(C); 42 USC 282(j)]
Public Notice of Noncompliance	No provision.	The NIH Director is to include a notification in the database if an RP fails to submit required clinical trials registry or results information. The notice is to state the nature of the noncompliance, note any penalties imposed under the act, and state whether the RP has corrected the information. If the RP failed to submit required information, the notice is to contain the statement "The entry for this clinical trial was not complete at the time of submission, as required by law. This may or may not have any bearing on the accuracy of the information in the entry." If the RP submitted false or misleading information, the notice is to contain the statement "The entry for this clinical trial was found to be false or misleading and therefore not in compliance with the law." If the RP failed to submit primary and secondary outcomes, the notice is to contain the statement "The entry for this clinical trial did not contain information on the primary and secondary outcomes at the time of submission, as required by law. This may or may not have any bearing on the accuracy of the information in the entry." The Director is to ensure that the public may search the database for entries that include noncompliance notices. [FDAAA 801(a)(2); PHSA 402(j)(5)(E); 42 USC 282(j)]
Authorization of Appropriations	Such sums as may have been necessary were authorized.	The amount of $10,000,000 per fiscal year is authorized for carrying out the clinical trials database provisions. [FDAAA 801(a)(2); PHSA 402(j)(7); 42 USC 282(j)]
Prohibited Acts	The law did not specify penalties or enforcement mechanisms related to registry requirements. General mechanisms for enforcing compliance with FDA requirements may have been applicable, but were not applied by the FDA.	The *prohibited acts* section of the FFDCA (21 USC 331) is amended, specifying that the following are illegal: (1) the failure to submit a certification or submitting a false certification of compliance with FDAAA's clinical trial database provisions; (2) the failure to submit FDAAA-required clinical trial information; and (3) the submission of FDAAA-required clinical trial information that is false or misleading in any particular. [FDAAA 801(b)(1); FFDCA 301(jj); 21 USC 331]

Topic	Previous Law	FDAAA Title VIII
Civil Monetary Penalties	The law provided general penalties for violations of prohibited acts, which FDA may have been able, but did not, apply to database infractions. Violators could be imprisoned for not more than one year or fined not more than $1,000, or both. Violators could be fined up to $10,000 if the violation occurred after a conviction under the applicable section, or with the intent to defraud or mislead.	Violators of FDAAA clinical trial database provisions may be subjected to not more than $10,000 for all violations adjudicated in a single proceeding, and not more than $10,000 per day for each day of violation after FDAAA-required notification of noncompliance is issued until the violation is corrected. [FDAAA 801(b)(2); FFDCA 303(f); 21 USC 333]
Investigational New Drug Informed Consent	Previous law contained informed consent requirements, but none specific to the registry.	FDAAA amends the FFDCA provisions pertaining to investigational new drugs (21 USC 355(i)), requiring the Secretary to update regulations to include in the informed consent documents and process a statement that clinical trial information has been or will be submitted for inclusion in the registry databank pursuant to FDAAA. [FDAAA 801(b)(3); FFDCA 505(b)(1); 21 USC 355(b),(i)]
Pediatric Postmarket Surveillance Guidance	No provision.	Within 12 months of enactment, the Secretary is to issue guidance on how the database requirements apply to a PMDSIA pediatric postmarket surveillance that is not a clinical trial. [FDAAA 801(c); 42 USC 282 note]
State Preemption	No provision.	No state or political subdivision of any 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);42 USC 282 note]
Rule of Construction	No provision.	The fact of submission of off-label use clinical trial information, if in compliance with PHSA 402(j) [revised registry and results database requirements], shall not be construed by the Secretary or in any judicial proceeding as evidence of a new intended use. The availability of compliant database submissions shall not be considered as labeling, adulteration, or misbranding under the FFDCA (21 USC 301 et seq.). [FDAAA 801(d)(2); 42 USC 282 note]

Title IX. Enhanced Authorities Regarding Postmarket Safety of Drugs

Title IX of FDAAA gives the FDA new authorities to ensure drug safety and effectiveness. These build on decades of incremental additions to FDA's regulatory scope and its ability to identify drug safety problems and to correct or minimize them.

For further information, see CRS Report RL32797, *Drug Safety and Effectiveness: Issues and Action Options After FDA Approval*, by Susan Thaul.

Since the 1938 passage of the FFDCA, the manufacturer of a new drug has had to demonstrate to FDA the product's safety before the agency would approve it for marketing in the United States. In 1962, the Harris-Kefauver Amendments to the FFDCA added product effectiveness to the premarket requirements. FDA cannot assert that any drug is completely safe. Instead, it considers whether, given the available information, the drug is safe enough when used correctly by the types of individuals and for the diseases or conditions for which it was tested. FDA and others must remain alert to new information as those drugs are used more widely because, until a very large number of individuals have taken a drug, a rare adverse effect may not occur or a very common condition may not be recognized as drug-associated.

Prior to FDAAA, the law allowed FDA to require a postmarket study as a condition of its initial approval of a marketing application, but did not authorize FDA to add such requirements after approval. The law did not allow FDA to require that manufacturers submit drug advertising material for review or approval before dissemination. Neither did it provide for civil penalties, authorizing only the revocation of approval or licensing (or the threat of revocation) to compel manufacturers to change labeling or advertising.

Subtitle A. Postmarket Studies and Surveillance

Subtitle A includes various provisions regarding postmarket studies and surveillance of human drugs. Its provisions do not apply to veterinary drugs.

Postapproval Studies and Clinical Trials

FDAAA authorizes the Secretary, under specified conditions after a drug is on the market, to *require* a study or a clinical trial. The Secretary may determine the need for such a study or trial based on newly acquired information. To require a postapproval study or trial, the Secretary must determine that (1) other reports or surveillance would not be adequate, and (2) the study or trial would assess a known serious risk or signals of serious risk, or identify a serious risk. The law directs the Secretary regarding dispute resolution procedures.

Labeling Changes

FDAAA authorizes the Secretary, upon learning of new relevant safety information, to *require* a labeling change. It also creates procedures, including time limits, for notification, review, dispute resolution, and violation, regarding labeling change requirements.

Risk Evaluation and Mitigation Strategies

FDAAA authorizes the Secretary to require, under specified conditions, a *risk evaluation and mitigation strategy (REMS)* at the time of a new application, after initial approval or licensing when a new indication or other change is introduced, or when the Secretary becomes aware of new information and determines a REMS is necessary. Any approved REMS must include a timetable of assessments.

The Secretary may include requirements regarding instructions to patients and clinicians, and restrictions on distribution or use (and a system to monitor their implementation). The law allows a waiver from REMS restrictions on distribution or use for certain medical countermeasures in the time of a declared public health emergency, and creates a mechanism to assure access to a drug with a REMS for off-label use for a serious or life-threatening disease or condition.

FDA practice has long included most of the elements that a REMS may include. FDAAA gives FDA, through the REMS process, the authority for structured follow-through, dispute resolution, and enforcement. These include required reviews of approved REMS at specified times initially and then as the Secretary determines; detailed procedures for the review of both proposed REMS and required or voluntary assessments or modifications; establishment of a Drug Safety Oversight Board; and evaluation of whether the various REMS elements assure safe use of a drug, and whether they limit patient access or place an undue burden on the health care system.

Enforcement

FDAAA expands the definition of *misbranding* to include the failure to comply with certain requirements regarding REMS, postmarket studies and clinical trials, and labeling. It establishes *civil monetary penalties* for violations of those requirements. The maximum for one violation is $250,000, up to $1 million for all violations within one adjudication proceeding. The law describes escalating penalties, based on continuing violations and efforts at correction, up to $10 million in a single proceeding.

Television Advertising

FDAAA creates a new FFDCA Section 503B to authorize the Secretary to require submission of a television advertisement to the Secretary for review before its dissemination. Based on this *review*, during which the Secretary may consider the impact the drug might have on specific population groups (such as older and younger individuals, or racial and ethnic minorities), the Secretary may recommend, but not require, changes in the ad. The law authorizes the Secretary to require that an ad include certain *disclosures* without which the Secretary determines that the ad would

be false or misleading. These disclosures concern information about a serious risk listed in a drug's labeling, and the date of a drug's approval.

An amendment to the FFDCA requires that television and radio ads present the required information on side effects and contraindications in a clear, conspicuous, and neutral manner (Section 502(n)).

A new FFDCA Section 303(g) establishes *civil penalties* for the dissemination of a false or misleading direct-to-consumer (DTC) advertisement. The amount is limited to $250,000 for the first violation in any three-year period, and to $500,000 for each subsequent violation in that period.

FDAAA requires a study by the FDA Advisory Committee on Risk Communication and a report to Congress from the Secretary regarding DTC advertising and its communication of health information and its effect on information access and health disparities among population subsets.

Active Surveillance and Assessment

FDAAA directs the Secretary to collaborate with public, academic, and private entities to develop a *postmarket risk identification and analysis system* using electronic databases. Detailed provisions require the Secretary to protect individually identifiable health information; consult the Drug Safety and Risk Management Advisory Committee; communicate with key stakeholders; coordinate with other drug safety data sources; and report to Congress. FDAAA authorizes the appropriation of $25 million for each of FY2008 through FY2012 in addition to funds available under PDUFA for these activities.

Information Dissemination

Various sections of Title IX of FDAAA, in addition to those described above, address the provision of health information. One required report to Congress must address how best to communicate risks and benefits to the public, including the use of REMS and whether to use a unique symbol in the labeling of a new drug or indication. Any published[25] DTC prescription drug advertisement must include a statement encouraging the reporting of negative side effects to FDA, along with a 1-800 number and website address. The Secretary must submit a report to Congress after studying whether the statement in printed advertisements is appropriate for television advertisements.

Funding

FDAAA authorizes increased appropriations to support components of the drug safety provisions. For the surveillance and assessment activities, the Secretary may use $25 million of PDUFA fees each year to carry out those activities. For REMS and other drug safety activities in this title, the new law increases the revenue

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[25] FDAAA does not define the term "published." In general, it appears to apply to printed, rather than broadcast, advertisements.

authorized under PDUFA by an additional $225 million over the period FY2008 through FY2012, and designates its use for drug safety activities.

Subtitle B. Other Provisions to Ensure Drug Safety and Surveillance

The provisions in Subtitle B of FDAAA Title IX address topics related to drug safety. The first section requires the Secretary to issue *guidance for the conduct of clinical trials of antibiotic drugs*; and convene a public meeting regarding orphan antibiotic products. A few sections address the physical security of drug products, such as requiring the Secretary to develop standards and technology to *protect the drug supply chain* against counterfeit and damaged drugs.

Other sections address communication with the public, expert committees, and others, about agency actions and plans. The Secretary must develop and maintain an *Internet Web site* with extensive drug safety information, and publish a list of all *authorized generic drugs*. The Secretary must provide *public access to action packages* for product approval or licensure,[26] including certain reviews; and establish an *Advisory Committee on Risk Communication*. The Secretary must refer an application for a new active ingredient to an *FDA advisory committee* or include in the action letter reasons for not doing so. FDAAA requires that the Secretary report on FDA's implementation of its plan to respond to recommendations in the IOM 2006 report *The Future of Drug Safety*.

The Secretary must also screen weekly the *Adverse Event Reporting System* database and report quarterly regarding new safety information or potential signals of a serious risk; report on procedures for addressing ongoing postmarket safety issues identified by the Office of Surveillance and Epidemiology; and annually review the backlog of postmarket safety commitments, report to Congress, and set relevant dates.

Finally, FDAAA prohibits the use in food of certain drugs or biological products, and prohibits the Secretary from delaying the review of generic drug applications on the basis of certain *citizen petitions*.

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[26] An action package is the compilation of FDA-generated documents, from the submission to final action, related to review of an NDA or efficacy supplement; documents pertaining to the format and content of the application generated during drug development; and labeling submitted by the applicant (FDA, "Action Packages for NDAs and Efficacy Supplements," at [http://www.fda.gov/cder/mapp/6020.8.pdf]).

Table 12. Law Created by *Enhanced Authorities Regarding Postmarket Safety of Drugs, Subtitle A (FDAAA Title IX, Subtitle A)*

Topic	FDAAA Title IX, Subtitle A
Postmarket Studies and Clinical Trials	No one may introduce a drug or biological product [hereinafter "drug"] into interstate commerce if its sponsor is in violation of the Secretary's requirement for postapproval studies or clinical trials, or requests for labeling changes related to safety. The Secretary may require a postapproval study or clinical trial on the basis of scientific data including information regarding a chemically or pharmacologically related drug. The purpose of a required postapproval study or clinical trial must be to assess a known serious risk or signals of serious risk, or to identify a serious risk. The Secretary may require a postapproval study or clinical trial after learning of new safety information. In requiring a study or trial, the Secretary must require a timetable and periodic reports. A sponsor that fails to comply with such requirements must demonstrate good cause. To require a postapproval study, the Secretary must determine that other reports or surveillance would be inadequate to assess a known serious risk, a signal of serious risk, or to identify unexpected serious risks. To require a postapproval clinical trial, the Secretary must determine that a postapproval study would be inadequate for the purpose. The sponsor may appeal a requirement to conduct a study or clinical trial by using dispute resolution procedures established by the Secretary. [FDAAA 901(a); FFDCA 505(o); 21 USC 355]
Labeling Changes	The Secretary may, upon learning of new relevant safety information, require that the sponsor submit a supplement for a labeling change. FDAAA creates procedures, including time limits, for notification, review, dispute resolution, and violation. It also authorizes the Secretary to accelerate timelines if the Secretary concludes that the labeling change is necessary to protect the public health. [FDAAA 901(a); FFDCA 505(o); 21 USC 355]
Risk Evaluation and Mitigation Strategies (REMS)	The introduction of a drug or biological product into interstate commerce is prohibited if its sponsor is not in compliance with any risk evaluation and mitigation strategy (REMS) required by the Secretary or fails to conduct a postmarket study required of a drug that received accelerated approval because it addressed a serious or life-threatening illness. [FDAAA 901(a); FFDCA 505(p); 21 USC 355]
REMS	The Secretary may require that the sponsor of a drug or biologic application or supplement to an application, including one for a new indication for use, submit a proposed REMS. The Secretary may require a REMS with fewer elements for a product under an abbreviated new drug application. *Pre-approval:* If the Secretary (acting through the office responsible for reviewing the drug and the office responsible for postapproval safety with respect to the drug) determines such a strategy is necessary to ensure that the benefits of the drug involved outweigh the risks of the drug, the Secretary may require a REMS. *Postapproval:* If the Secretary becomes aware of new safety information and determines a REMS necessary, the Secretary may require one. [FDAAA 901(b); FFDCA 550-1; 21 USC 355-1]

Topic	FDAAA Title IX, Subtitle A
REMS: Minimal Strategy	An approved REMS must include a timetable of assessments of the approved REMS. This includes an assessment no less frequently than at 18 months and again at 3 years after a drug is initially approved; in the seventh year; and, subsequently, at a frequency (including none, after the 3-year period following REMS approval) as the Secretary determines. [FDAAA 901(b); FFDCA 505-1; 21 USC 355-1]
REMS: Optional Elements	A REMS may include *information to patients*, to include Medication Guide and patient package insert, and a c*ommunication plan to health care providers*, such as letters, information about REMS, and explanations of safety protocols. [FDAAA 901(b); FFDCA 505-1; 21 USC 355-1]
REMS: Safe Access to Drugs with Known Serious Risks	The Secretary may require *restrictions on distribution or use*, along with a system to monitor implementation, based on the Secretary's evaluation of the elements needed to assure safe use. The restrictions may include required training and experience of the prescribing health care provider; special certification of providers or health care settings; dispensing limited to certain health care settings; evidence of safe-use conditions (such as laboratory results); patient monitoring; and patient enrollment in registries. The Secretary may waive any required restriction for use of certain medical countermeasures during a declared public health emergency. The Secretary must minimize burdens on patient access (e.g., a patient with a serious or life-threatening disease or condition, or one who lives in a rural or medically underserved area) to a drug and on the health care delivery system. FDAAA authorizes expanded access for an off-label use for a serious or life-threatening disease or condition. It also prohibits a sponsor from using a restriction on distribution to block or delay approval of a generic drug application. [FDAAA 901(b); FFDCA 505-1; 21 USC 355-1]
REMS: Assessments	A sponsor may submit a voluntary assessment of an approved REMS at any time. Assessments are required at prearranged times, and when the Secretary determines that new information indicates an existing element should be modified or included. The Secretary's determination must be based on new safety or effectiveness information. Required is an assessment of how well the elements to assure safe use are meeting the goal of increasing safe access to drugs with known serious risks and whether the goal or such elements should be modified; and an assessment of the status of required postapproval studies and clinical trials. [FDAAA 901(b); FFDCA 505-1; 21 USC 355-1]
REMS: Modifications	Modifications may be made that include the assessment timetable; or the addition, modification, or removal of a restriction on distribution or use. [FDAAA 901(b); FFDCA 505-1; 21 USC 355-1]

Topic	FDAAA Title IX, Subtitle A
REMS: Review and Dispute Resolution	The Secretary must promptly review each proposed REMS and each assessment of an approved REMS. The review must follow specified procedures, including timeframes. These include: dispute resolution, including review by a Drug Safety Oversight Board (made up of federal government scientists and health care practitioners), use of advisory committees, and administrative appeals; addressing drug class effects; and coordinating assessment timetables with efforts of other countries. A dispute resolution occurring before an initial approval must follow procedures set forth in the letters described in FDAAA 101(c). FDAAA creates a *Drug Safety Oversight Board* to be composed of scientists and health care practitioners who are federal employees and who the Secretary appoints. The Secretary must describe any required REMS or modification as part of an action letter on an application or in an order following an assessment. Such action letters and orders, and any deferrals, must be made publicly available. [FDAAA 901(b); FFDCA 505-1; 21 USC 355-1]
Regulation of Biological Products	An applicant for a biological product license must be subject to FFDCA Sections 505(o), 505(p), and 505-1. [FDAAA 901(c); PHSA 351; 42 USC 262]
Advertisements: Prereview	The Secretary may require a prereview (at least 45 days before dissemination) of any television advertisement for a drug. The Secretary may recommend changes that are necessary to protect the consumer, or that are consistent with prescribing information for the product under review; and, if appropriate, statements to include in advertisements to address the specific efficacy of the drug as it relates to specific population groups, including elderly populations, children, and racial and ethnic minorities. The Secretary is not authorized to make or direct changes in any material submitted pursuant to this subsection. The Secretary may, in formulating recommendations, take into consideration the impact of the advertised drug on elderly populations, children, and racially and ethnically diverse communities. [FDAAA 901(d)(2); FFDCA 503B; 21 USC 353b]
Advertisements: Required Disclosures	The Secretary may *require inclusion of a disclosure* in an advertisement if the Secretary determines that the advertisement would be false or misleading without a specific disclosure about a *serious risk* listed in the labeling of the drug involved. The Secretary may require, for not more than two years from approval, the advertisement to include a specific disclosure of the *approval date* if the Secretary determines that the advertisement would otherwise be false or misleading. [FDAAA 901(d)(2); FFDCA 503B; 21 USC 353b]
Advertisements: Statement of Side Effects and Contraindications	In a television or radio direct-to-consumer (DTC) advertisement of a drug that states the name of the drug and its conditions of use, the major statement relating to side effects and contraindications must be presented in a *clear, conspicuous, and neutral manner*. The Secretary must establish standards, by regulation, for determining whether a major statement meets those criteria. [FDAAA 901(d)(3); FFDCA 502(n); 21 USC 352(n)]

Topic	FDAAA Title IX, Subtitle A
Advertisements: Civil Penalties	FDAAA establishes civil penalties for the sponsor of a drug or biologic who disseminates a DTC advertisement that is false or misleading. It authorizes a civil monetary penalty not to exceed $250,000 for the first violation in any 3-year period, and not to exceed $500,000 for each subsequent violation in any 3-year period. No other civil monetary penalties in this act shall apply to a violation regarding DTC advertising. Repeated dissemination of the same or similar advertisement prior to the receipt of a written notice shall be considered one violation. After such notification, all violations under this paragraph occurring in a single day shall be considered one violation. The law directs how to consider publications published less frequently than daily, and specifies procedures, after the provision of written notice and opportunity for a hearing, regarding reviews, subpoenas, modifications, and judicial review. Civil penalties may not be assessed if the sponsor had submitted an advertisement for prereview and incorporated each comment received from the Secretary. If an applicant fails to pay an assessed civil penalty, the Attorney General may recover that amount plus interest. [FDAAA 901(d)(4); FFDCA 303(g); 21 USC 333]
Advertisements: Report	The Secretary must, with the advice of the Advisory Committee on Risk Communication and within two years of enactment, report to the Congress on DTC advertising and its ability to communicate to subsets of the general population. The Advisory Committee on Risk Communication must study DTC advertising as it relates to increased access to health information and decreased health disparities for these populations, and make recommendations in a report that the Secretary must submit to Congress. [FDAAA 901(d)(5)]
Effect on Pediatric Studies	Rule of construction states that this section is not to be construed as affecting the Secretary's authorities to request pediatric studies under FFDCA 505A or to require such studies under FFDCA 505B. [FDAAA 901(e); 21 USC 355a note]
Enforcement: Misbranding	FDAAA includes as *misbranding* the failure to comply with REMS requirements regarding assessments, additional elements included, or a restriction on distribution or use; or failure to comply with requirements relating to postmarket studies and clinical trials or labeling. [FDAAA 902(a); FFDCA 502(y,z); 21 USC 352]
Enforcement: Civil Penalties	An applicant who violates a REMS requirement or a requirement regarding postmarket studies or clinical trials or labeling is subject to a civil monetary penalty of not more than $250,000 per violation, and not to exceed $1 million for all such violations adjudicated in a single proceeding. If a violation continues after the Secretary provides notice of such violation to the applicant, the Secretary may impose a civil penalty of $250,000 for the first 30 days, doubling for every subsequent 30-day period, up to $1 million for one 30-day period, and up to $10 million for all such violations adjudicated in a single proceeding. The Secretary must, in determining the amount of civil penalty, consider whether the sponsor is making efforts toward correcting the violation. [FDAAA 902(b); FFDCA 303(f); 21 USC 333]
No Effect on Withdrawal or Suspension of Approval	The Secretary may withdraw the approval of an application or suspend the approval of an application without first ordering the applicant to submit an assessment of the approved REMS. [FDAAA 903; FFDCA 505(e); 21 USC 355(e)]
Benefit-Risk Assessments	The Commissioner must submit to Congress, within a year of enactment, a report on how best to *communicate to the public* the risks and benefits of new drugs and the role of the REMS in assessing such risks and benefits. As part of such study, the Commissioner shall consider the possibility of including in the labeling and any DTC advertisements of a newly approved drug or indication a *unique symbol* indicating the newly approved status of the drug or indication for a period after approval. [FDAAA 904]

Topic	FDAAA Title IX, Subtitle A
Active Postmarket Risk Identification and Analysis (APRIA): Develop Methods and Establish System	The Secretary must, in collaboration with public, academic, and private entities, develop methods to get access to data sources; develop validated methods set up a system to analyze safety data from multiple sources; and convene an expert committee to advise the Secretary on the development of tools and methods for the ethical and scientific uses for, and communication of, postmarketing data. Using the methods developed (above), the Secretary must establish a Postmarket Risk Identification and Analysis System and establish and maintain procedures to: use electronic health data for risk identification and analysis; provide standardized reporting of adverse event data; and use federal, private, and other data sources to conduct active adverse event surveillance and identify trends and patterns. In carrying out these activities, the Secretary must attend to timeliness of reporting, use of private sector resources, and development of other approaches to gathering drug safety data. [FDAAA 905(a); FFDCA 505(k)(3); 21 USC 355]
APRIA: Advanced Analysis of Drug Safety Data	The Secretary must establish collaborations with public, academic, and private entities to provide for advanced analysis of drug safety data to improve postmarket drug safety risk-benefit analysis, provide routine access to expertise, and enhance the Secretary's ability to make timely assessments. These analyses must protect individually identifiable health information. The Secretary must seek recommendations from the Drug Safety and Risk Management Advisory Committee and other FDA advisory committees regarding priority drug safety questions and mechanisms for answering them. The Secretary must establish procedures for the development of drug safety collaborations. The Secretary must provide the analyses, including their methods and results, about a drug to the drug's sponsor. Regarding contracts from the Secretary, FDAAA defines criteria by which entities can qualify, contract requirements, and other procedures. The Secretary must provide for appropriate communications with key public, scientific, public health, medical, and other key stakeholders; and, to the extent practicable, coordinate with activities of other entities that have drug safety data sources.[FDAAA 905(a); FFDCA 505(k)(4); 21 USC 355]
Disclosure of Data	Rule of construction states that this section is not to be construed to prohibit the lawful disclosure or use of data or information (such as individually identifiable health information) by an entity other than to protect privacy. [FDAAA 905(b); 21 USC 355 note]
Report to Congress	The Secretary must report to Congress on the use of the active postmarket risk identification and analysis system. [FDAAA 905(c)]
Authorization of Appropriations	To carry out the FDAAA-required risk identification and analysis activities for which funds are available under the prescription drug user fee program (FFDCA 736), FDAAA authorizes the appropriation of *an additional* $25 million for each of FY2008 through FY2012. [FDAAA 905(d)]
GAO Report	The Comptroller General must evaluate and report on data privacy, confidentiality, and security issues relating to the active postmarket risk identification and analysis system, and recommend actions, if necessary, to the congressional authorizing committees. [FDAAA 905(e)]
Advertisements: Toll-Free Number	Any published DTC advertisement must include the following statement printed in conspicuous text: "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." [FDAAA 906(a); FFDCA 502(n); 21 USC 352]
	The Secretary must, in consultation with the Advisory Committee on Risk Communication, study whether the statement required in *published* DTC advertisements is appropriate for *television* DTC advertisements; and report findings and determinations to Congress. If the Secretary determines that including the statement is appropriate, the Secretary must issue regulations to implement such a requirement. [FDAAA 906(b); 21 USC 352 note]

Topic	FDAAA Title IX, Subtitle A
No Effect on Veterinary Medicine	The provisions of this subtitle do not apply to a licensed veterinarian's use of drugs within a veterinarian-client-patient relationship. [FDAAA 907; 21 USC 355 note]
Authorization of Appropriations	FDAAA authorizes to be appropriated, for carrying out this subtitle and the amendments it made, $25 million for each of FY2008 through FY2012. This authorization is in addition to any other funds (see above) available for carrying out these activities. [FDAAA 908]
Effective Dates	All provisions in Subtitle A of Title IX begin 180 days after enactment. [FDAAA 909; 21 USC 331 note]

Table 13. Law Created by *Enhanced Authorities Regarding Postmarket Safety of Drugs, Subtitle B (FDAAA Title IX, Subtitle B)*

Topic	FDAAA Title IX, Subtitle B
Clinical Trial Guidance for Antibiotic Drugs	The Secretary must, within one year of enactment, issue guidance for the conduct of clinical trials with respect to antibiotic drugs, and review and update such guidance within five years of enactment. [FDAAA 911; FFDCA 511; 21 USC 360a]
Prohibition Against Food to Which Drugs or Biological Products Have Been Added	It is a prohibited act (under FFDCA Section 301, and therefore subject to FFDCA penalties) to introduce into food drugs or biologics that are either FDA approved/licensed or for which substantial clinical investigations have been instituted and made public, except in specified circumstances. [FDAAA 912; FFDCA 301(ll); 21 USC 331]
Pharmaceutical Security	The Secretary must develop standards and identify and validate effective technologies for the purpose of securing the drug supply chain against counterfeit, diverted, subpotent, standard, adulterated, misbranded, or expired drugs. The Secretary (in consultation with other federal agencies, including the Departments of Justice, Homeland Security, and Commerce, and manufacturers, distributors, pharmacies, and other supply chain stakeholders) must develop and prioritize standards for the identification, validation, authentication, and tracking and tracing of prescription drugs. The Secretary must develop a standardized numerical identifier to be applied to a prescription drug at the point of manufacturing and repackaging; address promising technologies, such as radiofrequency identification technology, nanotechnology, encryption technologies, and other track-and-trace technologies; undertake enhanced and joint enforcement activities with other federal and state agencies; and establish regional capabilities for validation and inspection. [FDAAA 913; FFDCA 505D; 21 USC 355e]
Citizen Petitions and Petitions for Stay of Agency Action (Regarding the Approval of Generic Drugs)	The Secretary may not delay the review or approval of generic or abbreviated new drug applications on the basis of a petition that seeks to have the Secretary take, or refrain from taking, actions relating to the application's approval. This prohibition is excepted when the Secretary determines that a delay is necessary to protect the public health. FDAAA provides detailed procedures involving determination by the Secretary; notification; format; public disclosure; denial based on intent to delay; final agency action; extension of petition period; certification and verification regarding the completeness of information submitted and whether and from whom payment is received; exhaustion of administrative remedies; and annual reports. [FDAAA 914; FFDCA 505(q); 21 USC 355]

Topic	FDAAA Title IX, Subtitle B
Postmarket Drug Safety Information for Patients and Providers	The Secretary must develop and maintain an Internet website with an extensive range of easily searchable drug safety information to allow patients and health care providers better access to information. The website must include links to other government sites; professional and patient labeling; FDA alerts, warning letters, guidance documents, and regulations; summaries of aggregate surveillance data; and the clinical trials registry and results data bank. At the later of 18 months after a drug's approval or after 10,000 individuals have used the drug, the Secretary must prepare a summary analysis of adverse drug reaction reports, including identification of any previously unidentified risks, potential new risks, or known risks reported in unusual number. The Secretary may contract with public and private entities to fulfill these requirements. The Advisory Committee on Risk Communication must review and evaluate the types of information on the website, and recommend ways to facilitate the dispensing of risk communication information to patients and providers. [FDAAA 915; FFDCA 505(r); 21 USC 355]
Public Access to Action Packages for Approval	Within 48 hours of an application's approval, the Secretary must publish on the FDA website a *summary review* that documents conclusions from all reviewing disciplines, noting critical issues and disagreements with the applicant and how they were resolved, recommendations for action and an explanation of any nonconcurrence with review conclusions. Within 30 days of an application's approval, the Secretary must publish on the FDA website (without disclosing trade secrets or confidential information) the *action package* for approval of a drug or licensure of a biologic, which includes: FDA-generated documents related to the review; documents pertaining to the application's format and contact that were generated during drug development; labeling submitted by the application; the summary review (described above); the Division Director and Office Director's decision document, which includes a brief statement of concurrence with the summary review, and a separate review of addendum if disagreeing with summary review or to add further analysis; and identification (with consent) of FDA participants in the decision. FDAAA declares that a scientific review of an application is considered the work of the reviewer and shall not be altered by management or the reviewer once final. [FDAAA 916; FFDCA 505(l); 21 USC 355(l)]
Risk Communication	The Secretary must establish an Advisory Committee on Risk Communication to include experts on risk communication, experts on specific risks, and representatives of patient, consumer, and health professional organizations. The Secretary must partner with nongovernmental groups to develop robust and multifaceted systems for communication to health care providers about emerging postmarket drug risks. [FDAAA 917; FFDCA 567; 21 USCbbb-6]
Referral to Advisory Committee	The Secretary must, before approving a drug that includes a new active ingredient, refer the drug to an FDA advisory committee. If referral is not made, the action letter on the application must include a summary of the reasons why the Secretary did not do so. [FDAAA 918; FFDCA 505(s); 21 USC 355]
Response to IOM 2006 Report	The Secretary must submit, within one year, a report updating FDA's implementation of its plan to respond to the recommendations in the IOM 2006 report *The Future of Drug Safety*, to include an assessment of FDA's implementation of REMS requirements. [FDAAA 919]

Topic	FDAAA Title IX, Subtitle B
Authorized Generic Drugs	The Commissioner must publish (within nine months of enactment) on the FDA website a list of all authorized generic drugs; update the list quarterly; and notify relevant federal agencies of those updates. An authorized generic drug is defined, for this section, as one that had previously been approved under FFDCA 505(c) and then "marketed, sold, or distributed directly or indirectly to retail class of trade under a different labeling, packaging (other than repackaging as the listed drug in blister packs, unit doses, or similar packaging for use in institutions), product code, labeler code, trade name, or trade mark than the listed drug." [FDAAA 920; FFDCA 505(t); 21 USC 355]
Adverse Drug Reaction Reports	The Secretary must conduct regular, biweekly screening of the Adverse Event Reporting System (AERS) database and post a quarterly report of any new safety information or potential signal of a serious risk identified by AERS within the last quarter. The Secretary must report within two years of enactment on FDA procedures and processes for addressing ongoing postmarket safety issues identified by the Office of Surveillance and Epidemiology (OSE) and how OSE recommendations are handled within the agency. The Secretary must annually review the entire backlog of postmarket safety commitments to determine which require revision or should be eliminated; report to Congress on these determinations; and assign start and estimated completion dates. [FDAAA 921; FFDCA 505(k); 21 USC 355]

Title X. Food Safety

Title X of FDAAA, entitled *Food Safety,* contains provisions designed to enhance FDA's authority and responsibilities to ensure the safety of the food supply. These were added to FDAAA after several widely reported outbreaks of food-borne illness that affected hundreds of individuals. In response, many members of Congress expressed concern about both domestic and imported food products and whether the current food safety system is adequate for handling the current globalized food supply.

As enacted, FDAAA requires the Secretary to establish processing and ingredient standards, update labeling requirements for pet food, and establish an early warning and surveillance system to identify adulteration and outbreaks of illness associated with pet food. The Secretary is to work with states to improve the safety of produce and strengthen state food safety programs. The Act requires the creation of a registry for reportable information on foods (including human and animal products) with safety problems that allows for the identification of the supply chain of the reportable food. Alerts are to be issued for such foods, with records maintained and available for inspection. Additional provisions require attention to aquaculture and seafood inspection, environmental risks associated with genetically engineered seafood products, imported foods, pesticide monitoring and ginseng dietary supplements.

This section was contributed by Donna V. Porter, Specialist in Nutrition and Food Safety, Domestic Social Policy Division.

For further information, see CRS Report RS22779, *Food Safety: Provisions in the Food and Drug Administration Amendments Act of 2007*.

Title XI. Other Provisions

Title XI of FDAAA, entitled *Other Provisions,* contains provisions relating to a number of topics. It is divided into two subtitles. *Subtitle A — In General* covers a range of topics: FDA employee publications, tropical disease treatments, genetic tests, NIH, and severability of FDAAA. *Subtitle B — Antibiotic Access and Innovation* focuses solely on that issue. Both are discussed below.

Subtitle A. In General

The first topic addressed in Subtitle A is agency clearance of employee scientific publications. The Secretary is required to establish and make publicly available clear written policies to implement the publication provisions. For FDA officers or employees who are directed by policy to obtain agency review or clearance prior to their work's publication or presentation, FDAAA provides a timeline for such review or clearance. Nothing in the policy is to be construed as affecting any restrictions on publication or presentation provided by other law.

The second topic addressed in Subtitle A is the introduction of a *priority review voucher* as an incentive to develop medical products that treat tropical diseases.

Qualifying diseases are those listed in the law, and any other infectious disease the Secretary designates by regulation. Diseases designated by regulation must disproportionately affect poor and marginalized populations, and must have treatments with no significant market in developed nations. The FDAAA provision adds a new use to the older FDA priority review mechanism. Rather than (or in addition to) providing the possible financial benefit of priority review to a sponsor for its tropical disease product application, FDAAA directs FDA to reward that sponsor for developing that product by giving it a priority review voucher that it can use for any one proposed subsequent product that would not otherwise qualify for priority review. The new provision further alters FDA's priority review mechanism by allowing the tropical disease product sponsor to transfer the voucher, including by sale, to another entity. The Secretary is to establish a user fee program and set the fee amounts for sponsors of human drug applications that are the subject of a priority review voucher.

The third topic addressed is the regulation of genetic testing. FDAAA requires that, if the specified Secretary's Advisory Committee does not complete and submit its report and recommendations regarding regulation and oversight of genetic testing to the Secretary by July 2008, the Secretary is to enter into a contract with the IOM to conduct a study and issue a report on the topic.

The fourth topic consists of technical amendments to sections of the PHSA (42 USC 201 et seq.), making five changes. Though the section is titled "NIH Technical Amendments," the first provision does not apply to NIH, but is rather a correction to P.L. 109-417, the Pandemic and All-Hazards Preparedness Act, and applies to the hospital preparedness program administered by the HHS Assistant Secretary for Preparedness and Response. The provision amends PHSA Section 319C-2 to make appropriate reference to the applicable funding formula for hospital preparedness and surge capacity grants.[27] The second provision adds minority health disparities to the types of data that the NIH Director is to assemble to assess research priorities. The third provision adds postdoctoral training funded through research grants to the list of research activities that the NIH Director is required to catalog in a biennial report to Congress. The fourth provision designates PHSA 403C (relating to the drug diethylstilbestrol) as 403D. The fifth provision specifies that each institution that receives an NIH award for training graduate students under its subchapter (PHSA, Title IV, Part A) need only report to NIH information regarding postdoctoral training funded through research grants, and not each degree-granting program at the institution. It further indicates that leaves of absence are to be subtracted when calculating the average time between graduate study and receipt of a doctoral degree.

The fifth topic addressed is severability. It directs that if any provision of FDAAA is found to be unconstitutional, the remainder of the Act shall remain in effect.

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[27] See CRS Report RL33589, *The Pandemic and All-Hazards Preparedness Act (P.L. 109-417): Provisions and Changes to Preexisting Law*, by Sarah A. Lister and Frank Gottron.

Subtitle B. Antibiotic Access and Innovation

FDAAA addresses antibiotic access and innovation by amending both the FFDCA and the PHSA. It also requires a GAO report assessing the effect of these provisions.

Under separate sections of the FFDCA, FDA both regulates antibiotics and provides incentives for the development of orphan drugs. FDAAA links those approaches by amending the Orphan Drug Act to require the Commissioner to consider (including convening a public meeting) which serious and life-threatening infectious diseases might be designated as rare diseases. If appropriate, the Secretary, by issuing new guidance, could designate product development activities for those diseases as qualifying for grants and contracts under the Orphan Drug Act. FDAAA also extends the Secretary's authority to issue grants and contracts for orphan drug development, and authorizes the appropriation of $30 million for each of FY2008 through FY2012.

FDAAA also adds a new subsection to FFDCA that allows a sponsor to consider as the same active ingredient a specific kind of chemical variant (a non-racemic drug) of an ingredient in an approved (racemic) drug. In addition, a separate provision of the law amends the PHSA to require the Secretary, through the Commissioner, to make publicly available clinically susceptible concentrations of bacteria (amounts that characterize the level of bacterial susceptibility and resistance to a drug).

Table 14. Comparison of *Other Provisions, Subtitle A (FDAAA Title XI, Subtitle A)* with Previous Law

Topic	Previous Law	FDAAA Title XI, Subtitle A
Policy on the Review and Clearance of Scientific Articles Published by FDA Employees	No parallel provision in 21 USC 371.	The Secretary is required to establish and make publicly available written policies to implement the publication provisions and govern the timely submission, review, clearance, and disclaimer requirements for articles. Article means a paper, poster, abstract, book, book chapter, or other published writing. An FDA employee or officer required by FDA policy to submit an article for review and clearance prior to publication or presentation must do so not less than 30 days in advance. Within 30 days, the reviewer may provide written clearance, which may contain the condition of specified changes. If the supervising official has not cleared or reviewed the article as of the 31st day after submission, the employee may consider the article not to have been cleared, and may submit or present it with an appropriate disclaimer. Nothing in the policy shall be construed as affecting any restrictions on publication or presentation provided by other law. [FDAAA 1101; FFDCA 713; 21 USC 379d-2]
Tropical Disease Priority Review	No provision.	The sponsor of an application for an eligible tropical disease product that is approved after FDAAA enactment shall receive a priority review voucher for use with a later application. Priority review is defined by FFDCA 735(1) to mean review and action by the Secretary on such application not later than 6 months after receipt by the Secretary of such application, as described in the FDA Manual of Policies and Procedures, and goals identified in the letters described in FDAAA 101(c). Qualifying diseases include tuberculosis, malaria, blinding trachoma, Buruli ulcer, cholera, dengue/dengue haemorrhagic fever, dracunculiasis (guinea-worm disease), fascioliasis, human African trypanosomiasis, leishmaniasis, leprosy, lymphatic filariasis, onchocerciasis, schistosomiasis, soil transmitted helmithiasis, and yaws. The Secretary may also include, by regulation, any other infectious disease that has no significant market in developed nations and that disproportionately affects poor and marginalized populations. The Secretary is to establish a user fee program and annually set the fee amount to be paid with the submission of the human drug application for which the voucher is used. [FDAAA 1102; FFDCA 524; 21 USC 360n]

Topic	Previous Law	FDAAA Title XI, Subtitle A
Improving Genetic Test Safety and Quality	No provision.	If the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) does not complete and submit the *Regulatory Oversight of Genetic/Genomic Testing Report and Action Recommendations* to the Secretary by July 2008, the Secretary shall enter into a contract with the IOM to conduct a study to assess the overall safety and quality of genetic tests and prepare a report that includes recommendations to improve federal oversight and regulations of genetic tests. The study is to take into account relevant reports by SACGHS and other groups, and to be completed not later than one year after the date the contract was entered. Nothing in the section is to be construed to require the delay of related federal regulatory efforts. [FDAAA 1103]
NIH Technical Amendments	Under P.L. 109-417, the *Pandemic and All-Hazards Preparedness Act*, regarding the hospital preparedness program administered by the HHS Assistant Secretary for Preparedness and Response, the amounts of awards to states and political subdivisions supporting partnerships for state and regional hospital preparedness to improve surge capacity was to be determined based upon PHSA 319C-1(h) [grants for real time disease detection improvement].	The amounts of appropriations awards to states and political subdivisions supporting *partnerships for state and regional hospital preparedness to improve surge capacity* is to be determined based upon the applicable funding formula for hospital preparedness and surge capacity grants (PHSA 319C-1(i)). [FDAAA 1104(1); PHSA 319C-2(j)(3)(B); 42 USC 247d-3b]
	The NIH Director was to assemble accurate data to be used to assess research priorities, including information to better evaluate scientific opportunity, public health burdens, and progress in reducing health disparities.	The NIH Director is to assemble accurate data to be used to assess research priorities including information to better evaluate scientific opportunity, public health burdens, and progress in reducing *minority and other* health disparities. [FDAAA 1104(2); PHSA 402(b)(4); 42 USC 282]
	The NIH Director was required to submit to Congress a biennial report consisting of, among other information, training activities, including investigator-initiated awards for postdoctoral training.	The NIH Director is required to submit to Congress a biennial report consisting of, among other information, training activities, including investigator-initiated awards for postdoctoral training *and postdoctoral training funded through research grants*. [FDAAA 1104(3); PHSA 403(a)(4)(C)(iv)(III); 21 USC 283]

Topic	Previous Law	FDAAA Title XI, Subtitle A
	The PHSA section relating to the drug *diethylstilbestrol* was the second of two sections numbered 403C.	The PHSA section relating to the drug *diethylstilbestrol* is redesignated as 403D. [FDAAA 1104(4); PHSA 403D; 21 USC 283a-3]
	Each institution receiving an award under this title [PHSA, Title IV] for the training of graduate students for doctoral degrees shall annually report to the NIH Director, with respect to *each degree-granting program* at such institution: (1) the percentage of students admitted for study who successfully attain a doctoral degree; and (2) for students described in paragraph (1), the average time between the beginning of graduate study and the receipt of a doctoral degree. (PHSA 403C(a)).	Each institution receiving an award under this title [PHSA, Title IV] for the training of graduate students for doctoral degrees shall annually report to the NIH Director, with respect to *its NIH-supported graduate students* at such institution: (1) the percentage of *such* students admitted for study who successfully attain a doctoral degree; and (2) for students described in paragraph (1), the average time (*not including any leaves of absence*) between the beginning of graduate study and the receipt of a doctoral degree. (Emphasis added). [FDAAA 1104(5); PHSA 403C(a); 42 USC 283a-2]
Severability Clause	No provision.	If any provision of FDAAA or the application of such provision or amendment is found to be unconstitutional, the remainder of the Act and amendments made by it and the application of the provisions of such to any person or circumstance shall not be affected thereby. [FDAAA 1105; 21 USC 301 note]

Table 15. Law Created by *Antibiotic Access and Innovation (FDAAA Title XI, Subtitle B)*

Topic	FDAAA Title XI, Subtitle B
Clinically Susceptible Concentrations	The Secretary, through the Commissioner, must identify and make publicly available clinically susceptible concentrations that characterize the level of bacterial susceptibility and resistance to a drug. [FDAAA 1111; 42 USC 247d-5a]
Orphan Drugs	The Commissioner must convene a public meeting and issue guidance, if appropriate, regarding which serious and life threatening infectious diseases might be designated as rare diseases, making drug development for treating such diseases eligible for assistance pursuant to the Orphan Drug Act (21 USC 360ee) or other incentives. [FDAAA 1112(a)]
	FDAAA reauthorizes grants and contracts for orphan drugs (21 USC 360ee), authorizing the appropriation of $30 million for each of FY2008 through FY2012. [FDAAA 1112(b); amends Sec. 5(c) of the Orphan Drug Act; 21 USC 360ee(c)]
Exclusivity of Certain Drugs Containing Single Enantiomers	An applicant for a non-racemic drug containing, as an active ingredient, a single enantiomer that is contained in a racemic drug approved in another application, may elect to have the single enantiomer considered the same active ingredient as that contained in the approved racemic drug, under certain circumstances. [FDAAA 1113; FFDCA 505(u); 21 USC 355]
GAO Report	The Comptroller General, by January 1, 2012, must report to Congress regarding the effect of provisions in this subtitle in encouraging the development of new antibiotics and other drugs; and in preventing or delaying timely generic drug entry into the market. [FDAAA 1114]

Appendix A. Authorized Appropriations

Table 16. Appropriations Authorized in FDAAA, FY2008-FY2012

(Dollars in thousands)

Purpose	FY2008	FY2009	FY2010	FY2011	FY2012
PDUFA Fees[a, b] [FDAAA 103(b), (e)(1); 21 USC 379h(b),(e)(3)]	$417,783	$427,783	$437,783	$447,783	$457,783
DTC Television Advertisement Review Fees[a, b] [FDAAA 104; 21 USC 379h-1(b),(g)(3)]	$6,250	$6,250	$6,250	$6,250	$6,250
MDUFA Fees[a] [FDAAA 212; 21 USC 379j(a)]	$48,431	$52,547	$57,014	$61,860	$67,118
Device Postmarket Safety [FDAAA 215]	$7,100	$7,455	$7,828	$8,219	$8,630
Grants for Improving Pediatric Device Availability [FDAAA 305; 42 USC 282 note]	$6,000	$6,000	$6,000	$6,000	$6,000
Program for Pediatric Studies of Drugs [FDAAA 502(b); 42 USC 284m]	$200,000	such sums as may be necessary			
Critical Path Public-Private Partnerships [FDAAA 603; 21 USC 360bbb-5(f)]	$5,000	such sums as may be necessary			
Clinical Trial Databases[c] [FDAAA 801(a); 42 USC 282(j)]	$10,000	$10,000	$10,000	$10,000	$10,000
Active Postmarket Risk Identification and Analysis [FDAAA 905(d); 21 USC 355 note]	$25,000	$25,000	$25,000	$25,000	$25,000
Postmarket Studies and Surveillance [FDAAA 908; 21 USC 355 note]	$25,000	$25,000	$25,000	$25,000	$25,000
Development of Orphan Drugs [FDAAA 1112(b); 21 USC 360ee(c)]	$30,000	$30,000	$30,000	$30,000	$30,000

a. This authorization is for the collection of user fees from private entities.
b. FY2009 - FY2012 fee amounts are baseline numbers to be adjusted annually based upon inflation, workload, rent, and other factors.
c. This authorization of $10 million per year continues indefinitely.

Appendix B. Action Items with Deadlines for Government Officials

The following chart contains a listing of FDAAA action items with deadlines for government officials. It is broken down by FDAAA title. Within each title, action items are listed by deadline. More detailed information regarding each of the items in the chart is available in the section of this report that corresponds to the title in which it is listed.

The following notes may be helpful to the reader. First, the chart includes federal agency personnel deadlines with specific dates only. It does not list deadlines for action by non-governmental personnel, though FDAAA includes many of these. Neither does it list required actions for federal agency personnel that have no specific deadlines, though FDAAA contains many of these as well. Second, for user ease, the title of the person required to take action is bolded. Third, for items that require action at regular intervals (such as annual reports), only the initial item is listed by date. The requirement for recurrence is specified in the text.

Table 17. FDAAA Action Items with Deadlines for Government Officials, by Title and Date

Deadline	Required Action
Title I: Prescription Drug User Fee Amendments of 2007	
October 1, 2007	**The Secretary** assesses and collects DTC television advertisement review fees. [FDAAA 104; 21 USC 379h-1]
October 27, 2007	**The Secretary** publishes initial Federal Register notice requesting any person to notify the Secretary within 30 days of the number of DTC television advertisements the person intends to submit for advisory review within FY2008. [FDAAA 104; 21 USC 379h-1]
December 26, 2007	**The Secretary** establishes DTC television advertisement review fee amounts for FY2008. [FDAAA 104; 21 USC 379h-1]
June 1, 2008	**The Secretary** publishes, annually, subsequent Federal Register notices requesting any person to notify the Secretary within 30 days of the number of DTC television advertisements the person intends to submit for advisory review within the next fiscal year. [FDAAA 104; 21 USC 379h-1]
August 1, 2008	**The Secretary** establishes, annually, DTC television advertisement review fee amounts for the next fiscal year. [FDAAA 104; 21 USC 379h-1]
January 28, 2009	**The Secretary** submits, annually through 2013, a PDUFA performance report and a PDUFA fiscal report to Congress. [FDAAA 105; 21 USC 379h-2]
November 1, 2009	**The Secretary** terminates, annually, DTC television advertisement review fee collection program if the total of operating reserves and fee revenues falls below a required amount. [FDAAA 104; 21 USC 379h-1]
January 15, 2012	**The Secretary** transmits recommendations for PDUFA reauthorization to Congress. [FDAAA 105; 21 USC 379h-2]
January 28, 2012	**The Secretary** refunds DTC television advertisement review fee amounts remaining in the operating reserve on a pro-rata basis. (Refunds occur earlier if DTC television advertisement fee collection program is terminated early). [FDAAA 104; 21 USC 379h-1]
Title II: Medical Device User Fee Amendments of 2007	
September 27, 2008	**The Comptroller General** submits to Congress a report on the appropriate use of the 510(k) process to determine whether a new device is safe and effective. [FDAAA 225]

Deadline	Required Action
September 27, 2008	**The Comptroller General** submits to Congress a report on nosocomial infections relating to medical devices. [FDAAA 229]
September 27, 2008	**The Secretary** submits to Congress a report on labeling information on the relationship between indoor tanning devices and the development of skin cancer or other skin damage. [FFDCA 230]
January 28, 2009	**The Secretary** submits, annually through 2013, a MDUFA performance report and a MDUFA fiscal report to Congress. [FDAAA 213; 21 USC 738A]
January 15, 2012	**The Secretary** transmits recommendations for MDUFA reauthorization to Congress. [FDAAA 213; 21 USC 738A]
Title III: Pediatric Medical Device Safety and Improvement Act of 2007	
December 26, 2007	**The Secretary** issues a request for proposals for grants or contracts to nonprofit consortia for demonstration projects to promote pediatric device development. [FDAAA 305; 42 USC 282 note]
September 27, 2008	**The Secretary** provides for annual review by the Pediatric Advisory Committee of pediatric devices exempted from HDE pricing restrictions. [FDAAA 303; 21 USC 260j(m)]
March 25, 2008	**The Commissioner** issues guidance for institutional review boards on how to evaluate requests to approve devices for which an exemption from HDE pricing restrictions has been granted. [FDAAA 303; 21 USC 360j note]
March 25, 2008	**The Secretary** submits to relevant congressional committees a plan for expanding pediatric medical device research and development. [FDAA 304; 42 USC 282(b)]
June 23, 2008[a]	**The Secretary** makes a determination on the grants or contracts to nonprofit consortia for demonstration projects to promote pediatric device development. [FDAAA 305; 42 USC 282 note]
March 27, 2009	**The Secretary** submits to relevant congressional committees the first annual report regarding pediatric medical devices. [FDAAA 302; 21 USC 360e-1]
January 1, 2012	**The Comptroller General** submits to relevant congressional committees a report on the impact of exempting qualifying devices from humanitarian device exemption pricing restrictions. [FDAAA 303; 21 USC 260j(m)]

Deadline	Required Action
Title IV: Pediatric Research Equity Act of 2007	
September 27, 2007	**The Secretary** requires that sponsors of assessments that result in specified labeling changes made pursuant to PREA distribute such information to health care providers. [FDAAA 402; 21 USC 355c]
October 27, 2007	**The Secretary** utilizes newly established internal review committee to provide consultation to reviewing divisions on specified pediatric plans and assessments. [FDAAA 402; 21 USC 355c]
September 27, 2008	Newly established internal committee conducts a retrospective review and analysis of PREA assessments submitted and deferrals and waivers granted since 2003. [FDAAA 402; 21 USC 355c]
September 27, 2010	**The Secretary** contracts with IOM to conduct a study and report to Congress regarding studies conducted pursuant to PREA or precursor regulations. [FDAAA 402; 21 USC 355c]
January 1, 2011	**The Comptroller General** submits to Congress a report that addresses the effectiveness of specified provisions (PREA and BPCA) in ensuring that medicines used by children are tested and properly labeled. [FDAAA 404]
Title V: Best Pharmaceuticals for Children Act of 2007	
September 27, 2007	**The Commissioner** puts into effect specified dispute resolution processes to be used when the Commissioner and sponsor have been unable to reach an agreement on appropriate labeling changes. [FDAAA 502(a)(1); 21 USC 355a]
September 27, 2007	**The Secretary** includes as a requirement of a written request that the sponsors of specified studies resulting in labeling changes reflected in the BPCA-specified annual review distribute, at least annually, such information to health care providers. [FDAAA 502(a)(1); 21 USC 355a]
September 27, 2007	**The Secretary** ensures that during the one-year period beginning on the date that a labeling change is approved pursuant to a specified provision of BPCA, all adverse events reports that have been received for the drug are referred to the OPT. During the following years, the Secretary refers reports as appropriate. [FDAAA 502(a)(1); 21 USC 355a]
September 27, 2007	**The Secretary** begins creating certain requirements for specified drugs for which pediatric studies have not been completed and for which there is a continuing need for information relating to their use in pediatric populations. [FDAAA 502(a)(1); 21 USC 355a]
January 1, 2008	Unless **the Commissioner** issues a final rule by this date, the proposed rule entitled *Toll-Free Number for Reporting Adverse Events on Labeling for Human Drug Products* takes effect. [FDAAA 502(f)]

Deadline	Required Action
September 27, 2008	**The Secretary** studies the feasibility of establishing a compilation of information on pediatric drug use and reports the finding to Congress. [FDAAA 502(b); 42 USC 284m]
September 27, 2008	**The Secretary** develops and publishes a priority list of needs in pediatric therapeutics. [FDAAA 502(b); 42 USC 284m]
September 27, 2010	**The Secretary** enters into a contract with the IOM to study and report to Congress regarding written requests made and the studies conducted pursuant to BPCA. [FDAAA 502(a)(1); 21 USC 355a]
Title VI: Reagan-Udall Foundation	
October 27, 2007	**The Secretary** convenes a meeting of the ex officio members of the Foundation's Board of Directors to accomplish specified purposes. [FDAAA 601; 21 USC 379dd]
March 27, 2009	**The Secretary** submits, annually, a report to Congress regarding critical path public-private partnerships. [FDAAA 603; 21 USC 360bbb-5]
September 1, 2009	**The Commissioner** submits, annually, to Congress a report summarizing the Foundation Director's annual report and other information. [FDAAA 601; 21 USC 379dd-2]
Title VII: Conflicts of Interest	
October 1, 2007	**The Secretary** determines the proportion of people who served as advisory committee members under specified conflict of interest exceptions in 2007. [FDAAA 701; 21 USC 379d-1]
February 1, 2008	**The Secretary** submits, annually, to relevant congressional committees a report with specified information about conflict of interest execptions made for advisory committee members. [FDAAA 701; 21 USC 379d-1]
September 27, 2012	**The Secretary**, not less than every 5 years, reviews guidance with respect to advisory committees. [FDAAA 701; 21 USC 379d-1]
Title VIII: Clinical Trial Databases	
December 26, 2007	**The Secretary** ensures that the registry data bank contains links to existing results of those trials that form the primary basis of an efficacy claim or are conducted after a product is approved or cleared, not later than 30 days after the results information becomes publicly available. [FDAAA 801(a)(2); 42 USC 282(j)(3)(A)(i)]

Deadline	Required Action
January 25, 2008[a]	**The NIH Director** ensures that clinical trial information is posted in the registry data bank for applicable trials initiated or ongoing as of December 26, 2007, to test drugs that treat life threatening diseases or conditions. [FDAAA 801(a)(2); 42 USC 282(j)(2)(C)(i) and (D)(i)]
September 27, 2008	**The Secretary** issues guidance on how the registry and data bank requirements apply to certain specified pediatric postmarket surveillance that is not a clinical trial. [FDAAA 801(c); 42 USC 282 note]
September 27, 2008	**The Secretary** includes basic results in the registry and results data bank for approved drugs, licensed biologics, and approved or cleared devices. [FDAAA 801(a)(2); 42 USC 282(j)(3)(C)]
October 27, 2008	**The NIH Director** ensures that clinical trial information is posted in the registry data bank for applicable trials of devices cleared or approved as of September 27, 2007. [FDAAA 801(a)(2); 42 USC 282(j)(2)(D)(ii)]
March 27, 2009	**The Secretary** holds a public meeting regarding the inclusion of expanded results in the registry and results data bank. [FDAAA 801(a)(2); 42 USC 282(j)(3)(D)(vii)]
March 27, 2009	**The NIH Director** ensures that the public may search the registry data bank by safety issue being studied. [FDAAA 801(a)(2); 42 USC 282(j)(2)(C)]
March 27, 2009	**The Secretary** determines, by regulation, the best method for including information on serious adverse events and frequent adverse events in the registry and results data bank. [FDAAA 801(a)(2); 42 USC 282(j)(3)(I)(i)]
September 27, 2009	If **the Secretary** fails to determine, by regulation, the best method for including information on serious adverse events and frequent adverse events in the registry and results data bank, a clause in FDAAA creating a regulation on the topic takes effect. [FDAAA 801(a)(2); 42 USC 282(j)(3)(I)(ii)]
October 27, 2009[a]	**The NIH Director** ensures that clinical trial information is posted in the registry data bank for applicable trials initiated or ongoing as of December 26, 2007, that test drugs that treat non-life threatening diseases or conditions. [FDAAA 801(a)(2); 42 USC 282(j)(2)(C)(iii) and (D)(i)]
September 27, 2010	**The Secretary** includes, by regulation, expanded results in the registry and results data bank. [FDAAA 801(a)(2); 42 USC 282(j)(3)(D)(i)]

Deadline	Required Action
Title IX: Enhanced Authorities Regarding Postmarket Safety of Drugs	
October 11, 2007	**The Secretary** screens, bi-weekly, the existing Adverse Event Reporting System (AERS) database. [FDAAA 921; 21 USC 355]
December 27, 2007	**The Secretary** posts quarterly reports of new safety information or potential signals of a serious risk identified by AERS. [FDAAA 921; 21 USC 355]
March 27, 2008	**The Secretary** conducts a study to determine whether a statement FDAAA requires for inclusion in published direct-to-consumer advertisements is appropriate for inclusion in television ads. [FDAAA 906(b); 21 USC 352 note]
June 27, 2008	**The Commissioner** publishes on FDA's website a complete list of authorized generic drugs; updates the list quarterly; notifies relevant federal agencies about the list and coming updates. [FDAAA 920; 21 USC 355]
September 27, 2008	**The Commissioner** submits to Congress a report on how best to communicate to the public the risks and benefits of new drugs and the role of risk evaluation and mitigation strategies in assessing such risks and benefits. [FDAAA 904]
September 27, 2008	**The Secretary** issues guidance for the conduct of clinical trials with respect to antibiotic drugs. [FDAAA 911; 21 USC 360a]
September 27, 2008	**The Secretary** submits annually to Congress a report on delays in approvals per citizen petitions for stays of agency action. [FDAAA 914(a); 21 USC 355]
September 27, 2008	**The Secretary** submits a report to Congress on ways to encourage the early submission of citizen petitions for stays of agency action. [FDAAA 914(b)]
September 27, 2008	**The Secretary** develops and maintains a website providing postmarket safety information for patients and providers. [FDAAA 915; 21 USC 355]
September 27, 2008	**The Secretary** issues a report responding to the 2006 IOM report: *The Future of Drug Safety — Promoting and Protecting the Health of the Public*. [FDAAA 919]
September 27, 2008	**The Secretary** annually reviews the entire backlog of postmarket safety commitments, determines which require revision or elimination, reports the determinations to Congress, and assigns start dates and estimated completion dates for the commitments. [FDAAA 921; 21 USC 355]

Deadline	Required Action
March 27, 2009	**The Comptroller General** evaluates data privacy, confidentiality, and security issues relating to active postmarket risk identification and analysis (APRIA), and makes recommendations to relevant congressional committees. [FDAAA 905(e)]
September 27, 2009	To prepare for the establishment of APRIA, **the Secretary** develops methods to access, link, and analyze safety data from disparate data sources, and convenes a committee of experts to make recommendations to the Secretary on the development of tools and methods for the ethical and scientific uses for, and communication of postmarketing data. [FDAAA 905(a); 21 USC 355]
September 27, 2009	**The Secretary** reports to Congress on FDA procedures and processes for addressing ongoing postmarket safety issues identified by the existing Office of Surveillance and Epidemiology, and how FDA handles recommendations of the Office. [FDAAA 921; 21 USC 355]
March 27, 2010	**The Secretary** establishes, by regulation, standards for determining whether a major statement in a direct-to-consumer advertisement relating to side effects is presented in the required manner. [FDAAA 901(d)(3); 21 USC 352 note]
March 27, 2010	**The Secretary** develops standard numerical identifiers to validate, authenticate, track and trace prescription drugs. [FDAAA 913; 21 USC 355e]
September 27, 2010[a]	**The Secretary** establishes and maintains the APRIA surveillance system as specified. [FDAAA 905(a); 21 USC 355]
March 26, 2011[a]	**The Secretary** establishes and implements procedures to contract with one or more qualified entities to classify or analyze aggregate APRIA data, allow for prompt investigation of priority drug safety questions, perform advanced research and analysis on identified drug safety risks, more effectively focus postapproval studies and clinical trials, and carry out other activities the Secretary deems necessary. [FDAAA 905(a); 21 USC 355]
September 27, 2011	**The Secretary** reports to Congress on the ways the Secretary has used APRIA to identify specific drug safety signals and to better understand the outcomes associated with marketed drugs. [FDAAA 905(c)]
September 27, 2012	**The Secretary** reviews and updates the guidance for the conduct of clinical trials with respect to antibiotic drugs. [FDAAA 911; 21 USC 360a]
Title X: Food Safety	
March 25, 2008	**The Secretary** submits a report to Congress on enhanced aquaculture and seafood inspection. [FDAAA 1006; 21 USC 2105]

Deadline	Required Action
June 1, 2008	**The Commissioner** submits, annually, to Congress a report concerning the results of the Administration's pesticide residue monitoring program. [FDAAA 1010; 21 USC 2109]
June 27, 2008	**The Secretary** issues a guidance to industry about submitting reports and providing notifications to other persons in the supply chain as required by regulations related to the Reportable Food Registry. [FDAAA 1005(f); 21 USC 350f note]
September 27, 2008	**The Secretary** establishes an early warning and surveillance system for pet food. [FDAAA 1002(b); 21 USC 2102]
September 27, 2008	**The Secretary** establishes a Reportable Food Registry. [FDAAA 1005(b); 21 USC 350f]
September 27, 2008	**The Secretary** submits, annually, to relevant congressional committees, a report with specified information about food regulation, inspection and importation. [FDAAA 1009; 21 USC 2108]
September 27, 2009	**The Secretary** establishes for pet food, by regulation, ingredient standards, processing standards, and updated labeling standards. [FDAAA 1002(a); 21 USC 2102]
Title XI: Other Provisions	
July 2008	If the Secretary's Advisory Committee on Genetics, Health, and Society does not complete and submit a specified report on the regulation of genetic testing, **the Secretary** enters into a contract with the IOM to conduct, by July 2009, a study of the safety and quality of genetic tests. [FDAAA 1103]
September 27, 2008	**The Secretary** may issue a priority review voucher to the sponsor of a tropical disease product. [FDAAA 1102; 21 USC 360n]
October 1, 2008	**The Secretary** establishes, annually, the amount of the priority review user fee. [FDAAA 1102; 21 USC 360n]
January 1, 2012	**The Comptroller General** submits to relevant congressional committees a report that examines specified effects of FDAAA's Antibiotic Access and Innovation provisions. [FDAAA 1114]

a. These dates are contingent on prior deadline(s). If an earlier task is completed prior or subsequent to the deadline specified in law, this date would be adjusted accordingly.

Appendix C. Authorities with Sunset Dates

Table 18. FDAAA Authorities with Sunset Dates

Authority (FDAAA Title)	Citation
Expiring October 1, 2012	
PDUFA fee collection (I)	FDAAA 106; 21 USC 379g note
DTC television advertisement fee collection (I)	FDAAA 106; 21 USC 379g note
MDUFA fee collection (II)	FDAAA 217; 21 USC 379i note
Third party review of premarket notification (II)	FDAAA 221; 21 USC 360m(c)
Pediatric device pricing exemption in humanitarian device exemption (III)	FDAAA 303; 21 USC 360j(m)
PREA pediatric study requirement (IV)	FDAAA 402; 21 USC 355c
BPCA pediatric market exclusivity (V)	FDAAA 502(a)(1); 21 USC 355a
Exclusivity of certain drugs containing enantiomers (XI)	FDAAA 1113; 21 USC 355
Expiring January 31, 2013	
PDUFA reporting requirements (I)	FDAAA 106; 21 USC 379g note
MDUFA reporting requirements (II)	FDAAA 217; 21 USC 379i note

Appendix D. Alphabetical List of Acronyms

APRIA	active postmarket risk identification and analysis
BPCA	Best Pharmaceuticals for Children Act (P.L. 107-109, reauthorized in FDAAA Title V)
CFR	Code of Federal Regulations
CRS	Congressional Research Service
DTC	direct-to-consumer (as in DTC advertising)
FDA	Food and Drug Administration
FDAAA	FDA Amendments Act of 2007 (P.L. 110-85)
FDAMA	FDA Modernization Act of 1997 (P.L. 105-115)
FFDCA	Federal Food, Drug, and Cosmetic Act (21 USC § 301 et seq.)
FNIH	Foundation for the National Institutes of Health
GAO	Government Accountability Office
HDE	Humanitarian Device Exemption
HELP	Senate Committee on Health, Education, Labor, and Pensions
HHS	Department of Health and Human Services
IOM	Institute of Medicine
MDUFA 2007	Medical Device User Fee Amendments of 2007 (FDAAA Title II)
MDUFMA	Medical Device User Fee and Modernization Act of 2002 (P.L. 107-250)
NIH	National Institutes of Health
OPT	Office of Pediatric Therapeutics, FDA
OSE	Office of Surveillance and Epidemiology, FDA
PDUFA I	Prescription Drug User Fee Act of 1992 (P.L. 102-571)
PDUFA II	the 1997 reauthorization of the Prescription Drug User Fee Act (P.L. 105-115, Title I)
PDUFA III	Prescription Drug User Fee Amendments of 2002 (P.L. 107-188, Title V)
PDUFA IV	Prescription Drug User Fee Amendments of 2007 (FDAAA Title I)
PHSA	Public Health Service Act (42 USC § 201 et seq.)
PI	principal investigator
PMA	Premarket Application (see MDUFMA and MDUFA 2007)
PMDSIA	Pediatric Medical Device Safety and Improvement Act of 2007 (FDAAA Title III)
PREA	Pediatric Research Equity Act of 2003 (P.L. 108-155, reauthorized in FDAAA Title IV)
QC	quality control
RP	responsible party
USC	United States Code