

## **A glimpse at the future Food and Drug Administration: A summary of the FDA Amendments Act of 2007.**

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On September 27, 2007, the President signed into law the FDA Amendments Act of 2007 one of the most significant changes to the Food and Drug Administration (FDA) in the past 20 years. This law will greatly impact the American public, healthcare providers as well as pharmaceutical and medical device companies. The Food and Drug Administration Amendments Act (FDAAA) is considered the most significant reform of the Federal Food, Drug, and Cosmetic Act (FFDCA) in years reauthorizing previous drug laws that were about to expire including Prescription Drug User Fee Act (PDUFA), Medical Device User Fee Act (MDUFA), Pediatric Research Equity Act (PREA) and the Best Pharmaceuticals for Children Act (BPCA) as well as making sweeping changes to how the FDA will operate in the future. The law responds to public criticism of FDA regarding drug safety particularly on the transparency of their decisions, the speed of their decisions and how they communicate those decisions to the American public. The law now requires FDA to establish an active drug risk surveillance system and grants FDA new authority to legally require product label changes, product post-approval clinical studies, risk management strategies called Risk Evaluation and Mitigation Strategies (REMS), and mandate specific disclosures in direct-to-consumer drug advertisements. The law also creates an expanded national clinical trial registry, clinical results data bank and addresses FDA advisory committee conflicts of interest.

### **Reauthorizing of the Prescription Drug User Fee Act (PDUFA)**

FDA Amendments Act of 2007 reauthorizes the Prescription Drug User Fee Act (PDUFA), which was to expire on September 30, 2007. The Prescription Drug User Fee Act (PDUFA) was first enacted in 1992, revised in 1997 and 2002, and is a program where the pharmaceutical/biotechnology industry pays certain "user fees" to the Food and Drug Administration (FDA). In exchange for these fees, the FDA agrees to a set of performance standards, i.e., to review and act on a manufacturer's market application within a certain time period with the overall goal to reduce the approval time for New Drug Applications (NDA) and Biological License Applications (BLA). The law currently assesses three types of user fees on manufacturers including fees for new product market applications (NDA/BLA); an annual fee on manufacturing plants and renewal fees for currently marketed products. Congress can increase the fees during the annual budget period but in return, FDA must devote a certain amount of the appropriated funds and resources to drug review activities. For example, the NDA/BLA application fee for 2008 is \$1,178,000 for an application requiring FDA to evaluate clinical data. The law now provides FDA with user fee revenue of approximately \$392.8 million for fiscal year 2008. FDAAA not only reauthorizes PDUFA, but also extends the original mandate for PDUFA by allowing FDA to use fees to fund new safety initiatives to expedite identification of safety signals and communication to public. This includes funding to improve collecting and reviewing safety information; developing adverse event data collection systems (e.g., IT systems); improved analytical tools to assess

potential safety problems including the use of public and private adverse event databases; enhanced oversight of manufactures to ensure compliance with post-marketing studies and label changes, and timely implementation of Risk Evaluation Mitigation Strategies (REMS).

### **Reauthorizing of the Medical Device User Fee Act (MDUFA)**

FDA Amendments Act of 2007 also reauthorizes the Medical Device User Fee Act (MDUFA), which was also set to expire. The MDUFA is similar to the PDUFA and was created for medical devices in 2002 with the same overall goal to reduce the approval time for Medical Devices. In exchange for fees, the FDA agrees to a set of performance standards, i.e., to review and act on a manufacturer's market application within a certain time. The law establishes three new types of fees for device manufacturers including an annual manufacturing plant registration fee, an annual fee for filing periodic reports required by a pre-market application (PMA) approval and a fee to make modifications to manufacturing procedures or methods of manufacture affecting the safety or effectiveness of a device. The law incorporates a number of changes intended to expand participation in the third-party inspection program including submission of audit reports assessing compliance with quality system standards set by the International Organization for Standardization (ISO). FDAAA also requires that FDA create regulations to establish a unique device identification system with a unique identifier in their labeling unless an exception for a certain device or type of device is granted. The new law encourages pediatric medical device research, to enhance the safety of those products and encourage the manufacture of special pediatric medical devices. The law also requires device manufactures to include in their applications a description of any pediatric subpopulations that suffer from the disease or condition that the device is intended to address.

### **Reauthorizing of the Pediatric Research Equity Act (PREA)**

The law reauthorizes the Pediatric Research Equity Act (PREA) but the Act will again expire in 2012. The Pediatric Research Equity Act gives FDA the authority to require pediatric studies of drugs for the drug's labeled indication only, i.e., when the pediatric use for the product would be the same as the approved adult use. Congress originally approved PREA in 1998, and for the first time established that certain new drugs and biologics must be tested for children and be available in formulations (e.g., liquids or chewable tablets) appropriate for children. The 1998 law was based on evidence that children's bodies may react to drugs much differently than adults, and that children can experience unique side effects not seen in adults. The FDA Amendment Act of 2007 continues to require safety and efficacy data in pediatrics for the same indication studied in adults and must be included for any new drug/biologic, indication, dosage form, and regimen or route application. Any new drug application or supplement must be accompanied by a pediatric assessment listing what studies are needed to evaluate the use of the drug in children for the disease studied. The manufacturer may request a deferral for those studies but must specify a timeline for completion of the pediatric studies. If the FDA grants a deferral, then the manufacturer must provide FDA with an annual information update detailing the progress made in conducting the studies. All this information is available to the public on the FDA's website. The manufacturer may also

request a waiver if the disease is not applicable to children, e.g., Alzheimer's Disease or if a pediatric formulation is not possible but are required to submit documentation supporting this position with the information again being made public on FDA's website.

### **Reauthorizing of the Best Pharmaceuticals for Children Act of 2007 (BPCA)**

The law reauthorizes the Best Pharmaceuticals for Children Act of 2007 (BPCA) for an additional five years. The BPCA was originally enacted in 2002 with a similar goal to PREA, i.e., to enhance drug research in children and provide healthcare professionals with information on the safe use of drugs in children. In exchange for specific pediatric research requested by the FDA, the BPCA grants the manufacturer an additional six months of marketing exclusivity for their product. However the new law now requires FDA to note on their website the specific drugs, the number and type of pediatric studies conducted, the pediatric formulations developed, and the product labeling changes made as a result of those studies.

### **Establishment of the Reagan-Udall Foundation**

The FDAAA legislation establishes the Reagan-Udall Foundation (Foundation), a nonprofit corporation to advance the mission of FDA to modernize medical product development, accelerate innovation, and enhance product safety.

### **Financial conflicts of interest in FDA advisory committee meetings.**

The new law now restricts the FDA's ability to grant waivers to permit participation of experts with financial conflicts of interest with drug/device manufacturers in FDA advisory committee meetings. The law specifies that FDA must decrease the number of waivers by 5% each fiscal year from 2008 to 2012 and disclose all waivers on FDA's website.

### **Expansion of the NIH Clinical Trials Database (Clinicaltrials.gov)**

The new law now expands the number and type of clinical studies that must be reported on the NIH's existing clinical trials registry (<http://clinicaltrials.gov>). It expands the types of drug trials that must be registered, extends registration requirements to medical devices, and establishes new results reporting rules. For all post-Phase I drug trials and medical device trials using a control comparator or conducted for pediatric post-market surveillance purposes, the drug sponsor must submit the following information for inclusion in the clinical trial registry data bank including the study title, purpose, study design, study phase, the study type, the primary disease or condition being studied, the intervention name and type, the study's start date, the expected completion date, the target number of enrolled subjects, and primary and secondary outcomes. In addition, recruitment information including eligibility criteria, location and contact information must be included. The law also requires FDA/NIH to expand the clinical trials registry database to include the results of the clinical trials that form the primary basis for the approval of a drug as well as the results for any clinical study conducted after the approval of the drug. All results are to be publicly available on the Internet. The clinical trial results data bank must also include links to the information related to clinical trials that support the approval of a product including FDA's approval documents and summaries of any FDA public health advisories. The law allows for civil penalties for

failure to comply with a maximum amount of \$10,000 for a violation. If the violation is not corrected in 30 days, then a penalty of \$10,000 for each day of the violation will be assessed until it is corrected.

### **New authority to require post-approval clinical trials or product label changes**

FDAAA also provides FDA with new authority to require post-approval clinical trials or make needed labeling changes for an approved medical product. FDA now has the authority to require a post-approval clinical trial of a product to assess a known serious risk, or signals of a serious risk, or to identify an unexpected serious risk. Studies or trials are only to be required if the FDA determines that current reporting process and the post market risk identification analysis system are not sufficient to address the concern. For each required study or trial, the FDA will require a timetable for its completion and periodic reports on status. If FDA becomes aware of new safety information regarding an approved drug or device from any source that may include ongoing clinical trials, post-approval studies, peer-reviewed literature, or post-market adverse event data, the FDA must notify the manufacturer of the approved product of their pending investigation. If FDA determines that the new safety information should be in the drug/device product labeling to guide healthcare providers as to the best use of the product, the manufacturer must submit a revised product label within 30 days of the notification. If FDA disagrees with the proposed product label changes, then discussions will continue for 30 additional days. However, within 15 days of the conclusion of the discussions, the FDA has the authority to issue an order directing the manufacturer to make a labeling change within an additional 15 days.

### **Creation of product risk evaluation and mitigation strategies**

The new FDAAA law provides FDA with a new tool to more fully characterize the risk benefit ratio for an approved or about to be approved product. FDA is now allowed to integrate “risk evaluation and mitigation strategies” (REMS) into their product reviews and post-market pharmacovigilance activities. This new program is really an evolution from previous FDA risk-management guidances and voluntary risk minimization plans called “Risk Minimization Action Plans”. The new law states that the FDA may require a REMS program if it is necessary to ensure that the benefits of the drug outweigh its risks. The FDA may also require REMS for new drugs/biologics, drugs and biologics that are currently being marketed, and for products seeking approval for a new usage. A manufacturer has 120 days to submit a REMS from the time it is notified by FDA and must include a timetable for the submission of assessments on the efficacy of the REMS (usually after 18 months, three years, and seven years). A REMS may include a medication guide and/or patient package insert for distribution to patients, and/or a communication plan to healthcare providers (e.g., sending letters disseminating information to healthcare providers directly or through professional organizations). The REMS may also have additional requirement for drugs with inherent toxicity or potential harmfulness including requiring prescribers have training or certification on the use of the product; a certification of the facilities that will dispense the drug; restrictions on the type of the healthcare facilities that may dispense/use the product; certification that the patient has been properly evaluated (e.g., laboratory tests); or require patient monitoring, e.g., “patient registry”. The REM may also require the sponsor/manufacturer to monitor,

evaluate, and improve on the overall effectiveness of the REM to ensure optimal risk/benefit for the use of the product. The law also provides civil monetary penalties of \$250,000 per violation, not to exceed \$1 million if a sponsor does not comply with a REMS requirement.

### **Review of direct-to-consumer advertisements**

The FDAAA authorizes the FDA to require the submission of any television advertisement for review 45 days before it is aired. The FDA may dictate wording that are necessary to protect consumers and are consistent with the product prescribing information. The new law requires any DTC television or radio advertisement present the drug's side effects in a clear, conspicuous, and neutral manner. Manufacturers will be subject to civil penalties for disseminating a false or misleading DTC advertisement. The new law caps the penalty at \$250,000 for the first violation in a three-year period, and \$500,000 for each subsequent violation in a three-year period.

### **Enhancement of FDA's post-market product risk identification and analysis capability**

The new law enhances the post-market product risk identification and analysis capability of the FDA and establishes an active post-market safety surveillance system using federal and private databases in addition to the current voluntary MedWatch adverse event-reporting program (<http://www.fda.gov/medwatch/how.htm>). The goal is to be able to secure and evaluate the safety data from 25,000,000 patients by 2010, and 100,000,000 patients by 2012 to enhance the ability of FDA to detect post-market risks for a product. This active adverse event surveillance will use federal health-related electronic data (e.g., Medicare and the Department of Veterans Affairs health systems), private sector health-related electronic data (e.g., pharmaceutical and health insurance databases) to identify adverse event trends and patterns. The FDA will also provide open communication of its safety activities to the public and must seek annual recommendations from the Drug Safety and Risk Management Advisory Committee regarding drug safety issues. The law requires FDA to conduct bi-weekly screenings of the Adverse Event Reporting System (AERS) database and post a quarterly report on the AERS website regarding any new safety information (<http://www.fda.gov/cder/drugSafety.htm>).

### **Enhanced communication of drug safety information to patients and healthcare providers**

FDAAA requires the creation of a website (<http://www.fda.gov/cder/drugSafety.htm>) with links to drug safety information for patients and healthcare providers. The website will be easily searchable and contain information from government websites, including the United States National Library of Medicine's Daily Med, Medline Plus, and FDA sites. The website will include labeling and package inserts, a link to Medication Guides, a link to the clinical trial registry and results data bank, the most recent FDA safety information and alerts, any Risk Evaluation Mitigation Strategies, and regulations related to drug safety. The website will provide access to summaries of known and serious side effects of drugs, and a summary analyzing the adverse drug reaction reports received for a drug for 18 months after a drug's approval. The website will permit patients and providers to submit adverse event reports on-line via the MedWatch system. The law

also requires that the FDA publish on their website a summary of the information that supports the approval of a drug/device application. The approval information must include documents generated by FDA during the product's review, the product labeling submitted by the applicant, a summary of the conclusions for each FDA reviewer and the FDA management conclusions regarding the approvability of the product.

In conclusion, the FDA Amendments Act of 2007 is one of the most significant changes to the Food and Drug Administration (FDA) in the past 20 years. This law reauthorizes previous drug laws that were about to expire including Prescription Drug User Fee Act (PDUFA), Medical Device User Fee Act (MDUFA), Pediatric Research Equity Act (PREA) and the Best Pharmaceuticals for Children Act (BPCA) as well as making sweeping changes as to how the FDA will operate in the future. The law responds to public criticism of FDA regarding drug safety particularly on the transparency of their decisions, the speed of their decisions and how they communicate those decisions to the American public. The law now requires FDA to establish an active drug risk surveillance system and grants FDA new authority to legally require product label changes, product post-approval clinical studies, risk management strategies, and mandate specific disclosures in direct-to-consumer drug advertisements. The law also creates an expanded national clinical trial registry and clinical results data bank and addresses FDA advisory committee conflicts of interest.