Food and Drug Administration Amendments Act of 2007 (FDAAA)
FDA Implementation – One Year After Enactment
September 2008

Summary:

The passage of FDAAA greatly increased the responsibilities of FDA as well as provided FDA with new authorities and reauthorized several FDA critical programs.

FDAAA reauthorized the Prescription Drug User Fee Amendments of 2007 (PDUFA) (Title I), the Medical Device User Fee Amendments of 2007 (MDUFA) (Title II), the Pediatric Research Equity Act of 2007 (PREA) (Title IV), and the Best Pharmaceuticals for Children Act of 2007 (BPCA) (Title V).

New pediatric medical device provisions were enacted in Title III as the Pediatric Medical Device Safety and Improvement Act of 2007.

An expanded clinical trials database was enacted in Title VIII which requires greater FDA involvement in ensuring that clinical trials information is provided to the National Institutes of Health (NIH) ClinicalTrials.gov.

The act, primarily Title IX, also provides FDA with additional requirements, authorities, and resources with regard to both pre- and postmarket drug safety. The statute contains important new authorities to require postmarket studies and clinical trials, safety labeling changes, and Risk Evaluation and Mitigation Strategies (REMS). The act requires increased activities for active post market risk identification and analysis particularly those related to tools and methods for data access and analysis. Title X of FDAAA also requires new reporting of adverse events related to food and new regulations for pet food labeling, ingredients, and processing standards.

FDAAA specified numerous deadlines for taking certain actions, including those for Congressional reports, guidances on various topics, regulations, and other regulatory actions. Many other provisions did not have specific deadlines.

In the year since enactment, FDA has implemented FDAAA as part of its public health mission devoting a significant amount of effort, resources, and time. The following list details the highlights of FDA's implementation activities.

FDAAA Implementation – Highlights
One Year After Enactment

Title I – Prescription Drug User Fee (PDUFA) Amendments

- Prescription Drug User Fee Rates of Fiscal Year 2008 published October 12, 2007.
- IT Planning per PDUFA goals letter – underway. Public meeting held October 19, 2007.
- New CDER employees hired ~ 657 since January (431 new hires); new CBER employees hired ~ 101 (64 new hires).
- Prescription Drug User Fee Rates for Fiscal Year 2009. (Published July 31, 2008.)
- Notice of Availability: Draft Prescription Drug User Fee Act IV Drug Safety Five-Year Plan. (Posted May 5, 2008)
- Prescription Drug User Fee Act IV Drug Safety Five-Year Plan (Draft). (Posted April 1, 2008)
- Draft Prescription Drug User Fee Act (PDUFA) IV Information Technology Plan. (Posted January 4, 2008)
- Concept paper for pilot study for industry to conduct their own name reviews in supporting their submission to the Agency posted for comment – completing final concept paper.

Title II – Medical Device User Fee Amendments

- Medical Device User Fee Rates for Fiscal Year 2008 published October 12, 2007.
- Guidance for Industry, Food and Drug Administration, and Foreign Governments: Fiscal Year 2008 Medical Device User Fee Small Business Qualification and Certification; published October 23, 2007; foreign businesses can now qualify as "small."
- FDA published a Notice in the Federal Register directing the public to the list of guidance documents CDRH is considering for development in the upcoming fiscal year and established a public docket for comments. October 2007, September 2008
- Implemented electronic registration and listing; this contributed to successful effort to update/correct R&L records — 13,700 establishments identified as inactive; establishment registration fees also meet statutory threshold.
- Guidance for Industry and FDA Staff: Interactive Review for Medical Device Submissions: 510(k)s, Original PMAs, PMA Supplements, Original BLAs, and BLA Supplements published December 2007 and updated February 2008 - To meet new performance goals, both FDA and regulated industry agreed that FDA should implement an interactive review process to encourage and facilitate

communication between FDA staff and industry during the review of medical device premarket submissions; staff are now trained and interactive review is standard operating procedure.

- Additional guidance documents published to facilitate smooth implementation of FDAAA-related requirements.
    - Establishing the Performance Characteristics of In Vitro Diagnostic Devices for the Detection or Detection and Differentiation of Influenza Viruses (February 15, 2008);
    - Expedited Review of Premarket Submissions for Devices (February 29, 2008); updated to reflect FDAAA.
    - FDA and Industry Actions on Premarket Approval Applications (PMAs): Effect on FDA Review Clock and Performance Assessment; (June 30, 2008); explains how FDA and industry actions affect MDUFA performance goals.
    - FY 2009 Medical Device User Fee Small Business Qualification and Certification; (August 1, 2008); the FY 2009 edition of this annual guidance, explains how to qualify for small business fee rates and fee waivers.
- Quarterly meetings with industry; we are now publishing the agenda and all FDA materials on web site simultaneous with the start of each meeting.

Title III – Pediatric Medical Device Safety and Improvement Act

- Draft Guidance to institutional review committees on how to evaluate requests for approval of exempted devices published August 5, 2008. (Section 303)
- Draft Pediatric Device Development Plan dated June 2008 published on NIH Pediatric Medical Devices Stakeholders Workshop website. An NIH, FDA, and AHRQ Working Group has met and developed preliminary plans and process. Public Meeting held on July 23, 2008. (Section 304)

Title IV – Pediatric Research Equity Act (PREA) and
Title V – Best Pharmaceuticals for Children Act (BPCA)

- Pediatric Review Committee (PeRC) established (internal review committee) – October 2007. (46 meetings held to date)
- PeRC has made 153 recommendations under PREA, reviewing assessments, plans, deferrals, and waivers (includes drugs and biologics). This accounts for:
    - 50 pediatric plans for PREA assessments
    - 64 PREA assessments
    - 50 deferral requests for PREA assessments
    - 108 PREA waiver requests

- PeRC has made 15 recommendations under BPCA, reviewing Written Requests, amended Written Requests, and inadequate proposed pediatric study requests. This accounts for:
    - 8 Written Requests
    - 5 Amended Written Requests
    - 2 Inadequate Letters
- Internal Processes established for expansion of safety reviews for PREA.
- 5 written requests for studies under BPCA have been issued; 3 are still pending.
- PREA and BPCA Labeling changes posted on website.
- 35 labeling changes since FDAAA enactment.
- Medical, statistical, and clinical pharmacology reviews of pediatric studies conducted in response to a Written Request issued under the BPCA (12) and pediatric assessments conducted under PREA (18) posted on website.
- Breakdown of Requested Studies Report; Written Requests Issued; Pediatric Exclusivity Granted; Pediatric Exclusivity Statistics; Spectrum of Diseases/Conditions – posted on FDA website.

Title VI – Reagan-Udall Foundation

- Foundation Established – October 2007.
    - Board appointed – November 2007; first board meeting – January 2008.
- Chief Scientist Appointed – April 2008. (Section 602)

Title VII – Conflicts of Interest

- Created templates to immediately implement provisions regarding conflicts of interest waivers and disclosure of financial information for Advisory Committee members.
- First annual Report to Congress on advisory committee vacancies and disclosures submitted for FY 2007 in May 2008.
- Public disclosures of financial interests and the justification for the waiver implemented immediately. Process is ongoing– all disclosures and waivers are posted on FDA's website. Federal Register notice announcing Final Guidance on Public Availability of Advisory Committee Members' Financial Interest Information and Waivers, including new templates for disclosure and waivers published on August 5, 2008.
- Final Guidance on Procedures for Determining Conflict of Interest and Eligibility for Participation in FDA Advisory Committees made available August 5, 2008. This guidance replaces FDA's 2000 Waiver Criteria guidance and incorporates a more stringent policy on considering waivers of conflict of interest as well as changes due to FDAAA.
- Administrative changes have been made to incorporate new requirements for all term appointments initiated after October 1, 2007; process is ongoing.

- Increased outreach and recruitment efforts to fill advisory committee vacancies. To date in fiscal year 2008:
  - Greater than 350 nominations received through FDA's advisory committee website for committee vacancies.
  - Contacted 269 professional organizations to recruit new members.
  - Mailed/e-mailed 371 communications seeking new nominees.
  - Attended 24 professional meetings seeking out new members.

Title VIII – Clinical Trial Databases

- Creation of 7 working groups with NIH to implement provisions of clinical trial registry and results database (FDA has been working with NIH, although most provisions are NIH's responsibility).
- Worked with NIH to implement first phase of "linking" information (information on FDA actions linked to clinical trials registry information). December 2007
- Developed FDA Certification Form in December 2007 to implement requirement that such form be submitted with FDA applications and submissions; published draft guidance in April 2008.

Title IX – Enhanced Authorities Regarding Postmarket Safety of Drugs

FDAAA provides FDA with additional requirements, authorities, and resources with regard to both pre- and postmarket drug safety. The statute contains important new authorities to require postmarket studies and clinical trials, safety labeling changes, and Risk Evaluation and Mitigation Strategies (REMS). The new safety authorities in Title IX, Subtitle A of FDAAA took effect on March 25, 2008.

- Between March 25 and September 9, 2008, FDA issued 21 letters for drugs and biologics requiring postmarketing studies, or clinical trials to address safety issues. In the past, these kinds of studies would have been undertaken voluntarily, as postmarketing commitments; now they are required, and the established timeframes for the conduct of the study are enforceable.
- FDA has used its new authorities to require safety label changes four times since March 25, 2008. All of the required safety label changes were invoked for classes of drugs or biologics. For example, FDA required sponsors of all conventional antipsychotic medications to add a Boxed Warning and other warnings to their prescribing information indicating a risk of mortality in elderly patients treated for dementia-related psychosis. FDA also required the makers of fluoroquinolone antimicrobial drugs for systemic use to add a Boxed Warning to their prescribing information indicating an increased risk of developing tendinitis and tendon rupture in patients taking their drugs. Sponsors of fluoroquinolones and antimicrobial drugs were also required to develop a Medication Guides for patients. FDA required sponsors of erythropoeisis stimulating agents (ESAs) to clarify the FDA-approved conditions for use of ESAs in patients with cancer and

revise directions for dosing to state the hemoglobin level at which treatment with an ESA should not be initiated. The most recent action was for the tumor necrosis factor (TNF) inhibitors to require that warnings about under recognition of histoplasmosis be added to the boxed warning and the Medication Guide.

- FDA can require REMS to ensure that the benefits of a drug outweigh its risks. Since March 25, 2008, FDA has approved 13 REMS, two of which have elements to assure safe use. The elements to ensure safe use involve certifications of prescribers and pharmacies and enrollment of patients in programs designed to ensure that all involved understand the risks associated with the products and the actions necessary to ensure their safe use. Eleven of the 13 approved REMS are REMS that only have Medication Guides and a timetable for assessment.
- On March 27, 2008, FDA issued a Federal Register notice to 24 sponsors that their products' were deemed to have REMS because they had risk management plans that had elements to assure safe use as defined in FDAAA. The sponsors are required to submit their REMS by September 21, 2008 to FDA. (Section 909)
- In May 2008, FDA launched the Sentinel Initiative. The ultimate goal of the initiative is to create and implement a nation-wide electronic system for monitoring medical product safety, the Sentinel System. Once in place, this new system will strengthen FDA's ability to monitor the performance of a product throughout the entire period of use, enhancing health protection. This system will satisfy the requirements of section 905, which directed FDA to develop methods to obtain access to disparate data sources and to establish a postmarket risk identification and analysis system. The law sets a goal of access to data from 25 million patients by July 1, 2010, and 100 million patients by July 1, 2012. The law also requires FDA to work closely with partners from public, academic, and private entities.
    - FDA has held 8 meetings with stakeholders to create broad forum for consideration of issues related to the creation and development of such a system. More meetings are planned.
    - FDA is soliciting work on 8 topics, including:
        - Developing a Governance and Operations Structure for the Sentinel Initiative
        - Engagement of Patients, Consumers, and Healthcare Professionals in the Sentinel Initiative
        - Defining and Evaluating Possible Database Models
        - Evaluation of Existing Methods for Safety Signal Identification
        - Evaluation of Potential Data Sources
- Multiple pilot projects are under way that will directly inform the Sentinel System. Among the pilots are the following:
    - OMOP (Observational Medical Outcomes Partnership with FNIH, FDA, PhRMA). Under a partnership involving FDA, the Foundation of the National Institutes of Health, and the Pharmaceutical Manufacturers of America, a series of experiments are being conducted to assess the value, feasibility, and utility of observational data to identify and evaluate the safety risks and potential benefits of prescription drugs. A range of analytical methods will be

used, applied against multiple observational data sources, in addition to currently available tools and data sources.

- FDA-CMS-ASPE Pilot on drug safety surveillance (using Medicare data). FDA and the Centers for Medicare & Medicaid Services (CMS), with the assistance of the Assistant Secretary for Planning and Evaluation (ASPE), have launched a pilot project that will use Medicare data to test the ability to confirm safety signals of specific drug products. The project will examine the effectiveness of analytic tools (e.g., data mining) to identify specific risks not apparent in the premarket safety database (e.g., multiple drug interactions, low probability adverse events).
- eHealth Initiative (Connecting Communities for Drug Safety Collaboration with HealthCare System and Regenstrief Institute/Indiana Network for Patient Care). FDA is serving as advisor on the eHealth Initiative (eHI) pilot study, which is exploring opportunities for using clinical information captured in the electronic databases of two large health information exchanges to identify and assess safety signals associated with marketed pharmaceuticals.

- Direct to Consumer (DTC) advertisements
  - FDAAA requires that we issue regulations on the standards for determining whether advertisements are clear, conspicuous, and neutral as it relates to side effects and contraindications. On August 6, 2008, we published a Federal Register notice on Agency Information Collection Activities published on August 6, 2008, for a study on distraction during the risk presentation in broadcast ads that will provide data relevant to establishing the "neutral" standard.
  - FDAAA requires that FDA, in consultation with the Advisory Committee on Risk Communication, report to Congress on the ability of DTC ads to communicate to subsets of the general population. On April 28, 2008, we published a Federal Register notice to obtain comments on issues related to report on Direct-to-Consumer Advertising including how it relates to communicating to subsets of the general population, and increased access to health information and decreased health disparities for these populations. On May 15, 2008, we met with the Advisory Committee to obtain their input on these topics. (Section 901)
  - FDAAA requires FDA to conduct a study in consultation with the Advisory Committee on Risk Communication, on the appropriateness of including, in televised DTC ads, a statement encouraging consumers to report negative side effects of prescription drugs to MedWatch (as is currently required for print DTC prescription drug ads). FDA has to report the findings of this and any plans to issue regulations to require the statement in TV ads to Congress. FDA met with the Advisory Committee on May 16, 2008, to obtain input on the proposed design of the study, and delivered an interim report to Congress on May 12, 2008. (Section 906)
- Issued three draft guidances on conducting clinical trials involving antimicrobials to treat acute bacterial sinusitis, antimicrobials to treat acute bacterial otitis media and acute bacterial exacerbations of chronic bronchitis in patients with Chronic

Obstructive Pulmonary Disease. (October 30, 2007, January 18, 2008, August 21, 2008) (Section 911)

- Prohibit the introduction into interstate commerce any food to which has been added certain drugs or biological products, unless the drug or biological product meets certain requirements. Federal Register Notice published on July 29, 2008; comments due October 27, 2008. (Section 912)
- Published two Federal Register requests for information on March 20, 2008, to support the development of standards for identification, validation, authentication, and tracking and tracing of prescription drugs. (Section 913)
- Thirteen Citizen Petitions have been completed in 180 days or less. All of the Citizens Petitions except one were completed by the deadline. (Section 914)
- Consolidated public website to list approved REMS and other safety information will be in place soon. (Section 915)
- Risk Communication Advisory Committee established: 3 RCAC meetings held in 2008. February 28-29, May 15-16, August 14-15. (Section 917)
- Section 919 of FDAAA requires FDA to conduct an assessment of how the FDA has implemented the recommendations described in the IOM report and the requirement under section 505-1(c)(2) of the Act (added by FDAAA) regarding working relationships between the offices responsible for reviewing and approving drugs and the offices responsible for monitoring postapproval safety. As required by FDAAA, FDA has used a team-based approach to making decisions about the need for and content of REMS. In CDER, team representatives from the Office of New Drugs (OND) and the Office of Surveillance and Epidemiology (OSE) work together in each case to determine the appropriate exercise of the new authorities. In addition, numerous other activities described below are under way to enhance the working relationships between these offices. Similarly, CBER has created cross-disciplinary teams who work collaboratively on implementing the FDAAA safety provisions. CDER and CBER are working together to ensure consistent implementation of FDAAA.
- Published FDA Listing of Authorized Generics on June 27, 2008. (Section 920)
- List of drugs and biologics from Adverse Event Reporting System (AERS) that FDA is investigating potential safety signal was posted September 5, 2008. This list will be updated on a quarterly basis. (Section 921)
- FDA is working with a contractor to eliminate the back-log of sponsors' postmarketing commitments. The teams are categorizing the open commitments and will issue a Federal Register notice in October 2008 to report on the status of the commitments. Furthermore, the public website for postmarketing commitments will include postmarketing requirements, which is one of the new authorities. (Section 921)

Title X – Food Safety

- Regulation for (1) Ingredient Standards and Definitions; (2) Processing Standards; and (3) Labeling Standards Including nutritional and ingredient information – Published Federal Register notice on April 21, 2008, seeking public comments on section 1002(a); Public meeting held on May 13, 2008. (Section 1002)
- FDA Consumer Complaint Reporting System (CCRS) is the Agency's present effective Early Warning System for pet food; FDA is actively promoting the CCRS to the veterinary profession through American Veterinary Medical Association and Veterinary Information Network (VIN).
- Initial plan to extend surveillance and response network created with variety of health officials at the Federal, State and Local Partners National meeting (50 State meeting) in August 2008 in St. Louis, Missouri.
- Work continuing on the Animal Feed Safety System (AFSS); public meeting was held on May 14, 2008.
- Reportable Food Registry Announcement of Delay in Implementation and Request for Comments published on May 27, 2008; comments were due on August 11, 2008. (Section 1005)
- FDA Pesticide Program Residue Monitoring 2004-2006 and Ginseng Dietary Supplements Special Survey (CFSAN Assignments and Field Regulatory Monitoring for FY 2003 and FY 2004) published August 4, 2008. (Section 1010)

Title XI – Other Provisions

- Draft Guidance for Industry on Tropical Disease Priority Review Vouchers under development. Public meeting is being planned. Notice expected in October establishing the amount of a priority review user fee for priority review voucher program. (Section 1102)
- Make available on FDA website any clinically susceptible concentrations (values that characterize bacteria) Federal Register Notice of Availability of Draft Guidance, *Updating Labeling for Susceptibility Test Information in Systemic Antibacterial Drug Products and Antimicrobial Susceptibility Testing Devices*, published on June 12, 2008; comment period closed August 11, 2008, comments under consideration. (Section 1111)
- April 28, 2008, Public Hearing held re: serious and life-threatening diseases due to antimicrobial resistance. (Section 1112)