



U.S. Department of Health and Human Services

Food and Drug Administration

Prescription Drug User Fee Act (PDUFA) IV Drug Safety Five-Year Plan

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DRAFT

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1.0 INTRODUCTION

The Prescription Drug User Fee Act (PDUFA) enacted in 1992 provided authority for FDA to collect additional resources (fees from industry) and enable FDA to accelerate its drug evaluation process without compromising review quality. Since 1992 PDUFA has seen a progression of performance commitments designed to speed drug development and approval while preserving and even raising FDA's high standards for safety, effectiveness, and product quality. Congress reauthorized PDUFA in 1997 under the FDA Modernization Act (FDAMA) and again in 2002 under the Public Health Security and Bioterrorism Preparedness and Response Act. Most recently Congress reauthorized PDUFA for another five years under the Food and Drug Administration Amendments Act of 2007 (FDAAA).

The original focus in the early years of the PDUFA program was getting quality products to market faster by significantly increasing the resources devoted to reviewing drug product applications and by requiring strict management and specific performance goals and targets. Beginning with PDUFA III in 2002, the PDUFA program was expanded to provide an increased focus on managing the risks of drug products that have been approved for marketing. PDUFA III authorized additional resources for risk management plan activities at pre-NDA and pre-BLA meetings, during the review of NDAs and BLAs, and during the period two-to-three years after approval. In addition, FDA met a PDUFA III goal by developing final guidance documents on good risk assessment, risk management, and pharmacovigilance practices¹. PDUFA IV authorizes a significant expansion of the post market focus under the PDUFA program.

Under the PDUFA IV program, \$29.29M (plus an annual inflation factor) will be allocated annually to enhance the Agency's drug safety capabilities. With these funds, FDA will be able to increase the number of employees dedicated to safety evaluation of marketed medications. FDA will also be able to add resources for adopting new scientific approaches to drug safety, reducing the risk of medication errors, improving the utility of existing tools for detection and prevention of adverse events, and incorporating the new approaches into the Agency's drug safety program.

2.0 PURPOSE

The purpose of this document is to communicate FDA's strategy for meeting the commitments for enhancing and modernizing the drug safety system within the context of the PDUFA IV program. FDA will use this plan to:

- Communicate strategies FDA will follow for using PDUFA IV drug safety resources;
- Communicate our current activity and establish measures to report progress; and
- Provide FDA leadership and management a foundation for understanding planned PDUFA IV drug safety activities.

3.0 ASSUMPTIONS

This five-year plan has been developed based on the assumption that FDA will receive additional fee revenues for "enhancement and modernization of the drug safety system" in the baseline

¹ The three guidance documents are titled "Pre-Marketing Risk Assessment," "Development and Use of Risk Minimization Action Plans," and "Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment."

amount of \$29.29M in FY 2008 with an annual inflation factor each year thereafter until FY 2012. We will refer to these funds as “PDUFA IV drug safety enhancement resources.” This plan reflects the Agency’s strategy for spending these drug safety enhancement user fees.

In addition to the \$29.29M, Congress authorized FDA to collect additional user fees to broaden the focus of drug safety in the FDA Amendments Act (FDAAA) of 2007. We believe that Congress intended these additional resources² to increase the Agency’s capacity for handling new authorities and requirements of FDAAA, including (as examples) efforts associated with implementing Risk Evaluation and Mitigation Strategies (REMS), Post-Market Study/Trial Requirements, Safety Labeling Changes, Active Postmarket Risk Identification, and other provisions. Attachment 1 provides a very brief summary of major new authorities and responsibilities enacted under FDAAA. We will refer to these funds as “FDAAA authorized resources.”

At this time, this plan does not include a strategy for spending the “FDAAA authorized resources”; rather it focuses only on the “PDUFA IV drug safety enhancement resources” intended to cover the negotiated drug safety commitments in the Department of Health and Human Services Secretary’s letters to the Chairman of the Committee on Health, Education, Labor, and Pensions of the Senate and the Chairman of the Committee on Energy and Commerce of the House of Representatives.

FDA will update this plan periodically (not less than annually) to make any adjustments required based upon actual annual amounts enacted by Congressional Appropriators and to include plans and strategies for spending the “FDAAA authorized resources”.

4.0 BACKGROUND AND CONTEXT

FDAAA for the first time recognizes FDA’s critical role in assuring the safe and appropriate use of drugs after they are marketed. PDUFA IV and FDAAA give FDA substantial new resources for medical product safety, as well as a variety of regulatory tools and authorities to ensure the safe and appropriate use of drugs. The Congress, consistent with many recommendations made over the past two years by the Institute of Medicine, the GAO, and a multitude of others, directs FDA to shift its regulatory paradigm to recognize that ensuring that marketed drugs are used as safely and effectively as possible is equally as important as getting new safe and effective drugs to market quickly and efficiently. With the goal of maintaining a systematic and scientific approach to the evaluation of benefit/risk throughout the product lifecycle, FDA must build the scientific and administrative capacity needed to become active and collaborative players in the U.S. healthcare delivery system.

Over the past decade, FDA has taken a number of critical steps to modernize the drug regulatory system, including: the Drug Quality Initiative for the 21st Century to institute a quality systems approach to cGMPs and other aspects of ensuring product quality; the Unapproved Drugs Initiative to make sure that all prescription and over-the-counter drugs marketed in the United States have been shown to be safe and effective; and, the Generic Initiative for Value and

² \$25,000,000 for FY 2008; \$35,000,000 for FY 2009; \$45,000,000 for FY 2010; \$55,000,000 for FY 2011; and \$65,000,000 for FY 2012.

Efficiency to help FDA modernize and streamline the generic drug approval process. Perhaps the most notable shift in drug regulation began in 1992 with the enactment of PDUFA. PDUFA implementation brought unprecedented accountability to the new drug review program, institutionalizing project management, prioritization and tracking for pre-market review activities. Drawing from lessons learned from each previous regulatory modernization initiative, FDA will now turn attention to transforming the post-market drug safety program.

5.0 PDUFA IV DRUG SAFETY COMMITMENTS

During negotiations with regulated industry on the post-marketing drug safety portion of the PDUFA IV program, FDA made commitments including:

- Developing and periodically updating a 5-year plan describing activities that will lead to enhancing and modernizing FDA's drug safety activities/system;
- Assessing current and new methodologies to collect adverse event information at various points during the product lifecycle;
- Identifying epidemiology best practices and developing guidance(s) describing these practices;
- Expanding database acquisition to be used for targeted post-marketing surveillance and epidemiology;
- Developing and validating risk management and risk communication tools; and
- Improving post-market IT systems.

The full text of the PDUFA IV commitments for enhancement and modernization of the drug safety system is provided as Attachment 2.

FDA also made commitments to increase the timely and consistent review of new drug trade names to prevent name confusion, including:

- Increasing consistency and scientific validity resulting in reduced medication errors associated with name confusion;
- Developing two new guidance documents to industry regarding: 1) contents of a complete submission package; and 2) best practices for naming, labeling and packaging;
- Establishing review goals and timelines;
- Conducting a pilot program to evaluate new Proprietary Name review paradigm; and
- Providing the public the full source code for the Agency's Phonetic and Orthographic Computer Analysis (POCA) tool (used by FDA to assess potential name confusion).

6.0 PDUFA IV STRATEGY FOR ENHANCING AND MODERNIZING THE DRUG SAFETY PROGRAM

FDA's strategy for enhancing and modernizing drug safety within the PDUFA IV program involves meeting its negotiated commitments summarized in Section 5.0. The following sections provide a description of the strategies FDA will pursue in meeting its commitments.

6.1 Strengthening Management and Operations

To better position its post-marketing safety program and to support and strengthen its post-market safety activities throughout the product life-cycle, FDA will increase the number of staff that focus on drug safety issues and post-market product surveillance.

The Center for Drug Evaluation and Research (CDER) has reorganized and is expanding its Office of Surveillance and Epidemiology (OSE), the office responsible for 1) monitoring post-market adverse event data to detect safety signals and evaluate risk; 2) developing, reviewing and analyzing observational pharmacoepidemiologic study protocols and results; 3) providing risk management expertise to the Center; and 4) medication error analysis and prevention activities, including the review of proposed product names, product labels and packaging for any potential to result in medication errors and the analysis of reports of medication errors. CDER is increasing the staff in OSE significantly in FY 2008. The new staff will be distributed across the office, strengthening the capability and capacity of the organization in its post-marketing safety role.

Similarly, the Center for Biologics Evaluation and Research (CBER) has taken steps to support and strengthen its post-market safety activities. CBER is increasing the staff in the Office of Biostatistics and Epidemiology for safety activities. In addition, since 2005, CBER has included a member of the Division of Epidemiology on all new vaccine BLA committees to review pharmacovigilance plans for post-marketing safety studies submitted by manufacturers. This activity expanded to other products areas in 2006 through 2008. CBER has also put in place interdisciplinary product safety teams for tissues, blood products, and vaccines, and will be expanding resources and FTEs to access and analyze health care databases in 2008.

With additional user fee funding, FDA will support and strengthen its post-market safety activities by increasing staff levels of:

- Safety evaluators who are responsible for reviewing adverse events reported for, and evaluating the safety of, marketed drugs;
- Epidemiologists who are responsible for reviewing protocols and study reports and conducting observational pharmacoepidemiological studies.
- Risk management experts to include additional risk management analysts, program evaluators, and behavioral and social science experts who are responsible for reviewing proposed and implemented Risk Minimization Action Plans (RiskMAPs) or Risk Evaluation and Mitigation Strategies (REMS) as well as reviewing and developing risk management communication tools;
- Medication error experts who are devoted to medication error analysis and prevention; and
- Regulatory project managers who are responsible for management, tracking, and facilitation of projects related to drug safety reviews, enhancing and improving communication, and providing regulatory input.

FDA will be focusing on recruiting and hiring these additional staff throughout FY 2008 and into FY 2009. Typically, it takes at least two to three years of intense training to prepare new staff to be seasoned experts in drug regulation.

6.2 Improving Collection and Analysis of Adverse Event Data

The goal of this public health initiative is to evaluate the impact of collecting and using spontaneous adverse event reports throughout the product life cycle on detection and characterization of drug safety risks and therefore supporting regulatory decisions to protect patient safety.

Spontaneous reporting provides valuable information for detecting adverse events, particularly those that are rare. However, under-reporting, the often poor quality of reports, and the lack of systematic feedback to healthcare providers and consumers may limit the full utility of the information. FDA will evaluate the impact of spontaneous reporting as a step in exploring and developing new strategies for surveillance. FDA research suggests safety-related regulatory actions occur throughout the life cycle of new drug products. Additional research in this area is needed to specifically address the role of spontaneous reports in safety-related regulatory decision making throughout the product life cycle. This research will investigate a range of questions related to the impact of the collection of adverse event information in regulatory decision making over the marketed life cycle of a product.

In January 2008, FDA held a public workshop entitled “Maximizing the Public Health Benefit of Adverse Event Collection Throughout a Product’s Marketed Life Cycle.” The purpose of the public workshop was to solicit information and views from interested persons on research approaches and methods associated with the best ways to assess the public health benefit of collecting and reporting all adverse events (AEs). The input from this workshop will be used to publish a request for information (RFI) to determine the types of outside organizations that would be interested in, and have the capability to conduct, this type of research. The request for information will be followed by a request for proposal (RFP).

This area of our strategy is focused on enhancing and modernizing our ability to detect “signals” of adverse events. FDA will establish a contract with external consultants to study the various mechanisms for collecting adverse events and determine optimal strategies for collecting adverse event data throughout the product life cycle.

6.3 Implementing Epidemiology Best Practices

Once FDA detects an adverse event “signal,” the Agency evaluates that signal to determine its validity (or strength) and its severity. FDA uses epidemiological data to quantify and characterize drug safety risks and to answer other questions of regulatory interest.

FDA will be focusing significant new resources and efforts into its capability and capacity to perform signal evaluation by developing good epidemiological practices guidance and by increasing its access to large electronic administrative databases.

Identifying Epidemiology Best Practices

In May 2008, FDA is seeking input from academia, industry, and others from the general public to identify best practices in epidemiology. The CDER and CBER will be holding a public workshop titled “Developing Guidance on Conducting Scientifically Sound Pharmacoepidemiologic Safety Studies Using Large Electronic Healthcare Data Sets.” The purpose of the public workshop is to solicit information and views from interested persons on

best practices and principles for the design and evaluation of pharmacoepidemiologic safety studies using large electronic healthcare data sets as one source of data.

FDA is committed to developing guidance to identify and encourage the use of best practices in the conduct of epidemiologic studies of drug safety issues by industry, FDA and academic researchers. With input received at the public workshop and other collaborations with external epidemiological experts, FDA will develop and issue draft guidance to address epidemiology best practices on carrying out scientifically sound observational studies using quality data sources. FDA's goal is to publish the draft guidance by the end of FY 2010 and final guidance by the end of FY 2011.

6.4 Expanding Database Acquisition and Use for Targeted Post-Marketing Surveillance and Epidemiology

Over the last several years, FDA obtained access, through contracts, to external data sources for drug use, patient outcomes, and special populations. In October 2005, the Agency awarded four contracts to Ingenix, Inc.; Kaiser Foundation Research Institute; The Vanderbilt University; and Harvard Pilgrim Health Care, Inc. that give the Agency access to databases containing pharmacoepidemiologic information and provide a mechanism for collaborative pharmacoepidemiological research designed to test hypotheses, particularly those arising from suspected adverse reactions reported to FDA.

Several other data sources accessed by FDA in recent years include:

- Longitudinal Outpatient Drug Utilization Database (Verispan) – to obtain national estimates of prescription use and patients associated with those prescriptions. This information is used to examine the extent of drug usage as well as patient exposure, patient demographics, patients' use of chronic therapies over time, and concomitant use of multiple therapies.
- IMS Health National Sales Perspectives (NSP) – provides data on drug products sold from manufacturer to various retail and non-retail settings. These data inform how risk management strategies should be targeted.
- Medicines Healthcare Regulatory Agency/General Practice Research Database (MHRA/GPRD) – currently FDA's only access to electronic medical records data which is the future direction of health care data and technology.
- Premier Healthcare Alliance – provides adult and pediatric comparative data on in-hospital drug use.
- Thomson and Thomson – provides trademark and copyright services and is used to help identify identical or confusingly similar names that may conflict with a specific trademark. These data are crucial to proprietary name and post marketing reviews.
- Center for Medicare and Medicaid Services (CMS) – conducted retrospective analysis of influenza and pneumococcal vaccine safety using CMS Part A and Part B data, as well as conducted a pilot evaluation of near real-time monitoring of seasonal influenza vaccine safety as part of pandemic influenza preparedness.
- Harvard University School of Public Health and Harvard Pilgrim Healthcare – accessed data from a large health care claims database to assess the safety of the annual influenza vaccine. Data were analyzed to simulate their accumulation in real time for targeted adverse events of interest showing the feasibility of near real-time assessment of influenza vaccine safety.

- Department of Defense/Army Medical Surveillance – data obtained to evaluate important vaccine safety issues.

In addition to expanding its access to these data sources, FDA will be using the additional new PDUFA IV funds to access new data sources and to conduct population based epidemiological studies. Examples of these expansions include:

- Entering into an inter-agency agreement with the Centers for Medicare and Medicaid Services (CMS) to access CMS Medicare data;
- Entering into an inter-agency agreement with the Veterans Health Administration (VHA) to access the VA’s large data repositories;
- Purchasing data reflecting drug usage in outpatient clinic/infusion centers and over-the-counter drug use data to access drug and biologic usage data and practice patterns of chemotherapeutics and other infused agents in hospital-affiliated and stand-alone outpatient clinics as well as infusion centers; and
- Substantially increasing funds for epidemiologic studies of adverse effects associated with marketed drugs.

6.5 Strengthening Risk Management and Communication Tools

FDA will develop a plan to identify, develop, and validate RiskMAPs and REMS elements including risk communication tools and will also conduct an assessment of their effectiveness. FDA will hold a public workshop to obtain input from industry and other stakeholders regarding the prioritization of the RiskMAPs, REMS, and communication tools to be evaluated, and will conduct annual, systematic, public discussion and review of the effectiveness of RiskMAPs, REMS, or communication tools. FDA will continue to conduct reviews of proposed and implemented RiskMAPs/REMS risk management plans to assess their effectiveness.

Last year, FDA created a new advisory committee designed to counsel the agency on how to strengthen the communication of risks and benefits of FDA-regulated products to the public. The new Risk Communication Advisory Committee will help FDA better understand the communication needs and priorities of the general public; advise FDA on the development of strategic plans to communicate product risks and benefits; and make recommendations to FDA on what current research suggests about crafting risk and benefit messages, as well as how to most effectively communicate specific product information to vulnerable audiences. Establishing the new Risk Communication Advisory Committee stems directly from the Institute of Medicine’s (IOM) 2006 report, *The Future of Drug Safety: Promoting and Protecting the Health of the Public*. FDA agreed with the value of such a committee and acted promptly to establish it. FDA also expanded the scope of the committee to cover communication of risks and benefits of all products regulated by the agency.

6.6 Improving Post-Market Information Technology Systems

Under the FDA Information Technology Target Architecture, IT solutions are organized into two categories: Common – meaning solutions that support the common business needs of the FDA; and Special Purpose – meaning IT solutions that support the business needs unique to a single business unit. Both Common and Special Purpose Post Market Information Technology Systems will be developed and implemented under PDUFA IV, including the MedWatch Plus Portal,

FDA Adverse Event Reporting System, the Sentinel System, and the Phonetic and Orthographic Computer Analysis (POCA) system. Additionally, FDA will leverage additional sources of scientific and administrative data for enhanced analysis of potential safety signals.

6.5.1 Update AERS and Modernize Adverse Event Reporting

To improve the timeliness and accuracy of the safety data collected through spontaneous reporting, FDA has endorsed a new strategic objective to institute a single internet portal for reporting an adverse event resulting from a FDA-regulated product. To support that objective, the Agency has initiated a new project, MedWatch^{Plus}, whose primary goal is to develop a user-friendly electronic submission capability for direct reports of safety information to FDA. This capability will facilitate submission of safety reports and better allow FDA to use the information to promote and protect the public health. This new agency-wide submission system will replace the current AERS data entry and electronic submission functionality.

Individual Case Study Report (ICSR)

A critical step toward automation of adverse event information is standardization of adverse event reporting. Until adverse event reporting is standardized, it will not be possible to link reported adverse event information with other clinical information nor to link pre- and post-market adverse event information.

The FDA, Centers for Disease Control and Prevention (CDC), and the National Institutes of Health (NIH) have been working with HL7³ on standards-based solutions for electronic adverse event reporting that meets the needs of all stakeholders. One outcome of these efforts is a new HL7 standard message for reporting adverse events, the HL7 Individual Case Study Report (ICSR) Release 2 Draft Standard for Trial Use, approved by HL7 in January 2007. This message standard supports both adverse event and product defect reporting for all FDA regulated products. The ICSR has the potential to dramatically improve adverse event reporting and analysis, by facilitating timeliness and reducing the cost of reporting, aggregation and analysis of possible product-related adverse events:

MedWatch^{Plus} Portal

The MedWatch^{Plus} Portal will provide a user-friendly internet portal for anyone to provide product safety information to FDA. It will improve the collection and processing of adverse event information for all FDA-regulated products and replace data entry/capture modules for current FDA adverse event report systems in order to provide enhanced structured data to improve the analytical value of received data. MedWatch^{Plus} will initially interface with various center adverse event reporting systems until FAERS implementation is complete.

FDA Adverse Event Reporting System (FAERS)

Adverse Event Reporting is a critical element of the Agency's post-marketing safety surveillance program for all FDA-regulated products. Currently, each Center has systems and processes that provide the FDA with safety data from various sources associated with the manufacture and use of regulated products. To improve the overall effectiveness of adverse event report analysis, the FDA is exploring the use of a single adverse event reporting repository for multiple regulated

³ Health Level Seven is one of several American National Standards Institute (ANSI) -accredited Standards Developing Organizations (SDOs) operating in the healthcare arena.

product types. FAERS will provide FDA with a modernized, comprehensive, state-of-the-art electronic system for adverse event report analysis that will incorporate safety signal detection, analysis, documentation and communication across FDA.

6.5.2 Sentinel System

The FDA, in coordination with other Federal agencies, is assembling an integrated “virtual” national medical product safety system -- the Sentinel System -- which would enable the electronic flow of safety information to and from the point of care. The system will build on existing public and private efforts through multiple, broad-based, public-private collaborations.

6.5.3 FDA Phonetic and Orthographic Computer Analysis (POCA) System: *Automated Method of Identifying Potential Look Alike and Sound Alike Proprietary and Established Names*

FDA developed a computerized method to determine orthographic (spelling) or phonetic (sound) similarities between proposed proprietary drug names that might increase the risk of confusion and medication errors. The POCA system is composed of two applications, POCA Search and Rx Studies. Under PDUFA IV, FDA will make the source code available to public parties for further development.

6.5.4 Collaborations with other federal agencies to share electronic health record data and administrative claims data for further analysis.

FDA will expand its access to safety information through collaboration with other federal agencies for the purpose of improving the FDA’s ability to conduct post-marketing safety assessments. For example, FDA has entered into a data use agreement with the Agency for Healthcare Research and Quality to use data from the Centers for Medicare and Medicaid Services to conduct a collaborative research project to develop data structures and methodologies for identifying and analyzing adverse drug events. FDA and the Veterans Health Administration have a memorandum of understanding to allow sharing of certain information related to the use of drugs, including vaccines and other biological products as well as medical devices. Access to data other than spontaneous reports would expand FDA’s capability to conduct targeted post-marketing surveillance, to look at effects of classes of drugs, and to detect signals.

6.7 Increasing Timely, Consistent Review of New Drug Trade Names to Prevent Name Confusion

FDA made several commitments regarding the review of new drug trade names. This section describes the strategies FDA will pursue to increase the timely and consistent review of new drug trade names to avoid potential name confusion between products.

6.7.1 Establishing review goals and timelines

FDA has had limited resources to perform trade name reviews of new drugs and therapeutic brand names. The current processes and practices result in long average review times. FDA is committed to reducing the review time of new drug trade names and, consistent with other PDUFA review metrics, is committed to managing the review of proprietary names according to the following targets:

Proprietary names submitted during IND phase (as early as end-of-phase 2)

- Review 50% of proprietary name submissions filed during FY 2009 within 180 days of receipt.
- Review 70% of proprietary name submissions filed during FY 2010 within 180 days of receipt.
- Review 90% of proprietary name submissions filed during FYs 2011 and 2012 within 180 days of receipt.

Proprietary names submitted with NDA/BLA

- Review 50% of NDA/BLA proprietary name submissions filed during FY 2009 within 90 days of receipt.
- Review 70% of NDA/BLA proprietary name submissions filed during FY 2010 within 90 days of receipt.
- Review 90% of NDA/BLA proprietary name submissions filed during FYs 2011 and 2012 within 90 days of receipt.

With additional resources from PDUFA IV, FDA will be able to increase the staff devoted to and responsible for the trade name review process. FDA will establish a working group with representatives from CDER and CBER to draft procedures and modify automated tracking systems to ensure that the Agency can meet the review targets set forth in the PDUFA IV commitment letter.

6.7.2 Developing New Guidance For Industry

FDA is committed to developing a guidance document for industry on the contents of a complete submission package for a proposed proprietary drug/biological product name. FDA has formed a working group with representatives from CBER and CDER and is writing guidance titled “Complete Submission for the Evaluation of Proprietary Names.”

A working group with members from CBER and CDER is also focusing on developing internal standard operating procedures for ensuring that internal procedures are consistent with meeting the proprietary name review goals. FDA expects to have the internal procedures available for staff by the end of FY 2009.

FDA is committed to developing guidance for industry on best practices for naming, labeling and packaging drugs and biologics to reduce medication errors. The Agency plans to consult with experts from academia, industry, and others from the general public to get input and feedback on best practices. FDA expects to publish draft guidance in FY 2010 and final guidance by the end of FY 2011.

The Agency plans to consult with experts from academia, industry, and others to get input and feedback on best practices for name evaluation. By the end of FY 2012, FDA expects to publish draft guidance on proprietary name evaluation best practices.

6.7.3 Conducting a Pilot Program

Within the PDUFA IV program, FDA committed to developing and implementing a pilot program to enable pharmaceutical firms participating in the pilot to evaluate proposed proprietary names and submit the data generated from those evaluations to the FDA for review.

FDA is in the process of preparing for a public meeting to be held in the late Spring to early Summer timeframe of 2008 to discuss and plan for a pilot program to be started later in the calendar year. The public meeting will include discussion of:

- Elements necessary to create a concept paper describing the logistics of the pilot program,
- Contents of a proprietary name review submission, and
- Criteria to be used by FDA to review submissions under the pilot program.

FDA expects to publish the concept paper by the end of FY 2008 and initiate and conduct the pilot program in FY 2009. After acquiring at least two years of experience during the pilot program, the FDA expects to conduct an assessment of the pilot, evaluating the experience and lessons learned.

6.7.4 Providing Full Source Code for Electronic Software

FDA is committed to providing the public the full source code for the Agency's Phonetic and Orthographic Computer Analysis (POCA) tool. POCA is an automated tool that FDA uses to assess potential name confusion between a new proposed product name and existing trade names. POCA includes a set of automated phonetic and orthographic algorithms that assist FDA in evaluating proprietary names for sound-alike or look-alike properties.

FDA is in the process of developing an optimal solution for providing the full source code and supporting technical documentation for POCA and expects to make it available for use by industry and others by the end of FY 2008.

7.0 APPLICATION OF PDUFA IV DRUG SAFETY ENHANCEMENT RESOURCES

To accomplish the strategies described in Section 6.0, FDA plans to apply the additional PDUFA IV fee revenues for “enhancement and modernization of the drug safety system” according to the following estimated schedule:

Strategy	Covers Activities in Section...	FY 2008	FY 2009	FY 2010	FY 2011	FY 2012
Support and strengthen post-market activities throughout the product life cycle	6.1, 6.2, 6.6	\$13.0M	\$13.5M	\$14.0M	\$15.0M	\$16.0M
Epidemiology Best Practices and Data Acquisition	6.3, 6.4	\$7.0M	\$7.5M	\$8.4M	\$9.0M	\$9.5M
Risk Management and Risk Communication	6.5	\$4.0M	\$4.2M	\$4.4M	\$4.6M	\$5.0M
New Drug Trade Name Review	6.7	\$5.3M	\$5.8M	\$6.2M	\$6.4M	\$6.5M
Total		\$29.3M	\$31.0M	\$33.0M	\$35.0M	\$37.0M

ATTACHMENTS

ATTACHMENT 1 – MAJOR NEW ACTIVITIES REQUIRED UNDER THE FDA AMENDMENTS ACT OF 2007

Key examples of major new activities required under FDAAA include:

- Risk Evaluation and Mitigation Strategy (REMS) - Consistent with our PDUFA III performance goals, FDA developed the concept of Risk Minimization Action Plans (RiskMAPs), which are described in the 2005 Guidance for Industry, Development and Use of Risk Minimization Action Plans. FDAAA now allows FDA to require a REMS at the time of approval, or after approval based on new safety information. The elements of a REMS are defined in the statute⁴. REMS elements include at a minimum a timetable for assessments of the REMS. In addition a REMS may include a Medication Guide and/or patient package insert and/or elements to assure safe use, which are what we commonly think of as restricted distribution. REMS can also require a communication plan to healthcare providers (i.e., dear healthcare practitioner letters, information about the REMS, or information through professional societies), but only for innovator products without generic competition (and not generics themselves).
- Post-Market Study/Trial Requirements - Before FDAAA, sponsors made commitments to conduct post-marketing studies and clinical trials. In certain limited situations (e.g., Subpart H accelerated approval), post-marketing clinical trials could be required as a condition of approval. In most cases, however, FDA requested sponsors to “voluntarily” commit to conducting the studies before approval, and had little recourse if they failed to conduct the agreed-upon study after approval. FDAAA allows FDA to require post-marketing studies or clinical trials at the time of approval or after approval based on new safety information, with criteria defined in the statute.
- Safety Labeling Changes – FDAAA includes new provisions regarding FDA’s responsibilities when new safety information becomes available that the Agency believes should be included in the labeling for the drug. FDA must notify a product sponsor if the Agency becomes aware of new safety information and must adhere to strict timelines for initiating and concluding discussions and ordering changes to the label. FDA will be developing procedures both for ensuring safety labeling changes are made as necessary and for determining how to handle violations of required changes should they occur.
- Active Postmarket Risk Identification and Analysis – FDAAA requires that FDA develop methods to obtain access to disparate data sources and to develop validated methods for establishing a postmarket risk identification and analysis system to link and analyze safety data from multiple sources. Further, FDAAA requires FDA to provide for active adverse event surveillance using several data sources including Federal health-related electronic data, private sector health-related electronic data, and other data necessary to identify adverse events and potential drug safety signals.

⁴ Elements to assure safe use include 1) healthcare providers who prescribe the drug have particular training or experience or are specially certified, 2) pharmacies, practitioners, or health care settings that dispense the drug are specially certified, 3) the drug be dispensed to patients only in certain health care settings, such as hospitals, 4) the drug be dispensed to patients with evidence or other documentation of safe-use conditions, such as laboratory test results, 5) each patient using the drug be subject to certain monitoring, or 6) each patient using the drug be enrolled in a registry.

- Other Significant Activities - FDAAA also specifically requires FDA to address many other areas such as reporting how best to communicate risks and benefits of new drugs to the public, addressing citizen petitions, requiring pre-review of television advertisements, meeting new requirements for holding Drug Safety Oversight Board meetings, and many other activities.

ATTACHMENT 2 – PDUFA IV COMMITMENTS FOR ENHANCEMENT AND MODERNIZATION OF THE DRUG SAFETY SYSTEM

- FDA will develop and periodically update a 5-year plan describing activities that will lead to enhancing and modernizing FDA’s drug safety activities/system.
 - FDA will publish a draft of the plan by March 31, 2008.
 - FDA will solicit and consider comments from the public on the draft plan. The public comment period will be at least 45 calendar days.
 - FDA will complete revisions to the plan and publish the final version no later than December 31, 2008.
 - By the end of FY 09, FDA will conduct an annual assessment of progress against the plan to be published on the FDA website.

- Assess current and new methodologies to collect adverse event information at various points during the product lifecycle;
 - By the end of FY 08, FDA will publish a Request for Proposals (RFP) to solicit proposals from outside research organizations to conduct research on determining the best way to maximize the public health benefit associated with collecting and reporting serious and non-serious adverse events occurring throughout a product’s life cycle.
 - Contract(s) will be awarded during FY 09 and completion of study(ies) targeted for FY11.

- Identify epidemiology best practices and developing guidance(s) describing these practices;
 - During FY 08, the FDA, with input from academia, industry, and others from the general public, will hold a public workshop to identify epidemiology best practices.
 - By the end of FY 10, CDER and CBER jointly will develop and issue a draft guidance document that addresses epidemiology best practices and provides guidance on carrying out scientifically sound observational studies using quality data resources.
 - A final guidance will be issued in FY 11.

- Expand database acquisition and use for targeted post-marketing surveillance and epidemiology;
 - Obtain access to additional databases, to train existing staff, and to hire additional epidemiologists and programmers to be able to use these new resources.

- Develop and validate risk management and risk communication tools, including assessing the effectiveness of risk management plan agreements and developing, implementing, and evaluating mechanisms for public communications about the benefits and risks of drugs and biological products;
 - During FY 08, FDA will develop a plan to 1) identify, with input from academia, industry, and others from the general public, risk management tools and programs for the

purpose of evaluation and 2) conduct assessments of the effectiveness of identified Risk Minimization Action Plans (RiskMAPS) and current risk management and risk communication tools.

- A public workshop will be held during FY 09 to obtain input from industry and other stakeholders regarding the prioritization of the plans and tools to be evaluated.
- Starting in FY 09, FDA will conduct annual systematic public discussion and review of the effectiveness of one to two risk management program(s) and one major risk management tool. Reports of these discussions will be posted on the FDA website.
- Improve post-market IT systems (e.g., AERS 2, safety tracking system, and opportunities for linked data management).
 - FDA will establish the following standards-based information systems to support how FDA obtains and analyzes post-market drug safety data and manages emerging drug safety information:
 - Enhanced adverse event reporting system and surveillance tools;
 - IT infrastructure to support access and analyses of externally-linked databases; and
 - Workflow tracking system.
 - Enhance and improve communication and coordination between OSE and OND, including activities to assess the impact and value of routinely including post-market review staff on pre-market review teams

IX. REVIEW OF PROPRIETARY NAMES TO REDUCE MEDICATION ERRORS

To enhance patient safety, FDA will utilize user fees to implement various measures to reduce medication errors related to look-alike and sound-alike proprietary names and such factors as unclear label abbreviations, acronyms, dose designations, and error prone label and packaging design.

A. Review Performance Goals – Drug/Biological Product Proprietary Names

1. Proprietary names submitted during IND phase (as early as end-of-phase 2)

- a) Review 50% of proprietary name submissions filed during FY 09 within 180 days of receipt. Notify sponsor of tentative acceptance or non-acceptance.
- b) Review 70% of proprietary name submissions filed during FY 10 within 180 days of receipt. Notify sponsor of tentative acceptance or non-acceptance.
- c) Review 90% of proprietary name submissions filed during FYs 11 and 12 within 180 days of receipt. Notify sponsor of tentative acceptance or non-acceptance.
- d) If proprietary name is found to be unacceptable, sponsor can request reconsideration by submitting a written rebuttal with supporting data or request a meeting within 60 days to discuss the initial decision (meeting package required).

e) If proprietary name is found to be unacceptable, the above review performance goals also would apply to the written request for reconsideration with supporting data or the submission of a new proprietary name.

f) Complete submission is required to begin the review clock.

2. Proprietary names submitted with NDA/BLA

a) Review 50% of NDA/BLA proprietary name submissions filed during FY 09 within 90 days of receipt. Notify sponsor of tentative acceptance/non-acceptance.

b) Review 70% of NDA/BLA proprietary name submissions filed during FY 10 within 90 days of receipt. Notify sponsor of tentative acceptance/non-acceptance.

c) Review 90% of NDA/BLA proprietary name submissions filed during FYs 11 and 12 within 90 days of receipt. Notify sponsor of tentative acceptance/non-acceptance.

d) A supplemental review will be done meeting the above review performance goals if the proprietary name has been submitted previously (IND phase after end of phase 2) and has received tentative acceptance.

e) If proprietary name is found to be unacceptable, sponsor can request reconsideration by submitting a written rebuttal with supporting data or request a meeting within 60 days to discuss the initial decision (meeting package required).

f) If proprietary name is found to be unacceptable, the above review performance goals apply to the written request for reconsideration with supporting data or the submission of a new proprietary name.

g) Complete submission is required to begin the review clock.

3. Guidance Document Development

a) By the end of FY 08, FDA will publish a final guidance on the contents of a complete submission package for a proposed proprietary drug/biological product name.

b) By the end of FY 09, FDA will prepare a MaPP (Manual of Policies and Procedures) to ensure that FDA internal processes (e.g., Division of Medication Errors and Technical Support, Division of Drug Marketing, Advertising, and Communications, Office of New Drugs, CDER and Advertising and Promotional Labeling Branch, CBER) are consistent with meeting the proprietary name review goals.

c) By the end of FY 10, after public consultation with academia, industry, and others from the general public, FDA will publish a draft guidance on best practices for naming, labeling and packaging drugs and biologics to reduce medication errors. Final guidance will be published by the end of FY 11.

d) By the end of FY 12, after public consultation with industry, academia and others from the general public, FDA will publish a draft guidance on proprietary name evaluation best

practices. Publication of final guidance on proprietary name evaluation best practices will follow as soon as feasible.

B. Pilot Program

During PDUFA IV, FDA will develop and implement a pilot program to enable pharmaceutical firms participating in the pilot to evaluate proposed proprietary names and submit the data generated from those evaluations to the FDA for review.

1. FDA will hold a public technical meeting to discuss the elements necessary to create a concept paper describing the logistics of the pilot program, the contents of a proprietary name review submission, and the criteria to be used by FDA to review submissions under the pilot program. Subsequently, by the end of FY 08, FDA will publish the concept paper.
2. By the end of FY 09, FDA will begin enrollment into the pilot program.
3. By the end of FY 11, or subsequent to accruing two years of experience with pilot submissions, FDA will evaluate the pilot program.

C. Other Activities

1. FDA and industry are interested in exploring the possibility of “reserving” proprietary names for companies once the names have been tentatively accepted by the Agency. By the end of FY 08, FDA will initiate a public process to discuss issues around “reserving” proprietary names.
2. FDA will provide the full source code and supporting technical documentation for the Phonetic and Orthographic Computer Analysis (POCA) tool and make it available on disk for use by industry and others from the general public by end of FY 08.