



THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

November 7, 2011

The Honorable Joseph R. Biden, Jr.
President
United States Senate
Washington, DC 20510

Dear Mr. President:

Enclosed for your consideration is the Food and Drug Administration's (FDA's) report to Congress required by section 921 of the Food and Drug Administration Amendments Act (FDAAA). FDAAA requires FDA to submit a report to Congress regarding internal procedures and processes for addressing ongoing postmarket safety issues identified by the Office of Surveillance and Epidemiology (OSE) and how recommendations of the OSE are handled within the Agency.

The following report summarizes procedures and processes that FDA has developed and implemented since the passage of FDAAA. These processes collectively aim to improve the working relationship between the offices responsible for reviewing and approving drugs and those responsible for monitoring safety during the postmarket period.

Maintaining the safety and effectiveness of drugs regulated by FDA has always been a critical component of the Agency's mission to protect and promote the public health. This report highlights the Center for Drug Evaluation and Research's (CDER) commitment to fully integrate OSE's expertise and areas of responsibility into CDER to help ensure the safety of marketed drug products. CDER has invested substantial resources to make certain that postmarket safety issues identified by OSE, or any other office in CDER, are fully vetted through use of the new authorities and resources provided by FDAAA. This report also highlights the many activities underway to refine existing processes and develop new policies and procedures for safety issue identification, assessment, and decision-making.

I hope you find this information on the status of our efforts helpful.

Sincerely,

A handwritten signature in black ink that reads "Kathleen Sebelius". The signature is written in a cursive, flowing style.

Kathleen Sebelius

Enclosure



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WASHINGTON, D.C. 20201

November 7, 2011

The Honorable John Boehner
Speaker of the House of Representatives
Washington, DC 20515

Dear Mr. Speaker:

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November 7, 2011

The Honorable Michael B. Enzi
Ranking Member
Committee on Health, Education, Labor, and Pensions
United States Senate
Washington, DC 20510

Dear Senator Enzi:

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The Honorable Tom Harkin
Chairman
Committee on Health, Education, Labor, and Pensions
United States Senate
Washington, DC 20510

Dear Mr. Chairman:

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November 7, 2011

The Honorable Fred Upton
Chairman
Committee on Energy and Commerce
U.S. House of Representatives
Washington, DC 20515

Dear Mr. Chairman:

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November 7, 2011

The Honorable Henry A. Waxman
Ranking Member
Committee on Energy and Commerce
U.S. House of Representatives
Washington, DC 20515

Dear Representative Waxman:

Enclosed for your consideration is the Food and Drug Administration's (FDA's) report to Congress required by section 921 of the Food and Drug Administration Amendments Act (FDAAA). FDAAA requires FDA to submit a report to Congress regarding internal procedures and processes for addressing ongoing postmarket safety issues identified by the Office of Surveillance and Epidemiology (OSE) and how recommendations of the OSE are handled within the Agency.

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Report to Congress
FDA Initiatives to Address and Manage Ongoing Postmarket Safety Issues
Identified by the Office of Surveillance and Epidemiology

Department of Health and Human Services
Food and Drug Administration
2011

Submit to HHS for review and concurrence before final signature:

 Date: SEP 23 2011
Margaret A. Hamburg, M.D.
Commissioner of Food and Drugs

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Executive Summary

Section 921 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) requires that the Food and Drug Administration (FDA or the Agency) submit a report to Congress regarding internal 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.

FDA's Center for Drug Evaluation and Research (CDER) has developed and is using a uniform, team-based approach for addressing and managing ongoing postmarket drug safety issues, whether identified by OSE, the Office of New Drugs (OND), or any other office in CDER.

Prior to drug approval:

- OSE's review roles and responsibilities have been formally integrated into the full pre-approval process (i.e., while the new drug application is still under review) (see III. G. 1.).
- An OSE division now has signatory authority for all decisional letters regarding proprietary name reviews; a policy issuance guides CDER staff through this process (see III. G. 2.).
- OSE plays an active role in developing and reviewing postmarket requirements and commitments and in reviewing risk evaluation and mitigation strategy (REMS) submissions while a new drug application is still under review (see III. G. 3. and 4.).

Following drug approval:

- OSE and OND hold regular joint meetings to address specific drug safety issues (see III. C.).
- OSE, OND, and other CDER offices form collaborative, multi-disciplinary review teams to manage significant postmarket safety issues and track their progress; a software tool was specifically designed to assist staff in managing and archiving significant postmarket safety issues (see III. D. and E.).
- CDER has established center-wide policies and procedures to foster a collaborative environment for decision-making, emphasizing open communication and the full participation of all relevant disciplines and organizational components (see III. F.).
- OSE and OND collaboratively perform extensive evaluations of new drugs and summarize and publicly post their findings, as specified by Section 915 of FDAAA (see III. H.).
- When new safety information about a marketed drug triggers the need for a sponsor to propose a REMS, implement safety labeling changes, or conduct postapproval studies or clinical trials, OSE joins with representatives from OND and several other CDER offices to collaboratively review and act upon the new information (see III. H.).

- OSE works with OND and external epidemiology research investigators to complete in-depth safety studies, the results of which inform FDA's regulatory decision-making process and enhance drug safety assessments (see III. I.).
- OSE leads the CDER-wide implementation of the new capabilities stemming from the creation of the FDAAA-mandated Sentinel System. OSE created a CDER-wide steering committee to address the procedures involved with submitting and prioritizing drug-related safety queries, guidelines for their review, and considerations for interpreting the results along with safety information from other sources (see III. J.).
- OSE leads or is closely involved in various efforts to communicate drug safety information to the public. FDA posts a quarterly report to its Adverse Event Reporting System Web site of any new safety information or potential signal of a serious risk. OSE has been engaged with staff throughout the Agency in designing various communication formats and contributes expertise on an ongoing basis to timely and formal public drug safety communications (see III. K.).

Working to ensure the safety and effectiveness of drugs regulated by FDA has always been a critical component of the Agency's mission to protect and promote the public health. This report highlights CDER's commitment to assure that OSE's expertise and areas of responsibility are fully integrated into CDER processes in an environment favorable to ensuring the safety of marketed drug products. CDER has invested substantial resources to ensure that postmarket safety issues identified by OSE, or any other office in CDER, can be fully vetted through the utilization of the new authorities and resources provided by FDAAA. This report highlights the many activities underway to refine existing processes and develop new policies and procedures for safety issue identification, assessment, and decision-making.

I. Introduction

On September 27, 2007, Congress passed FDAAA¹. The landmark drug safety provisions of FDAAA gave FDA important new drug safety authorities and also directed the Agency to establish a variety of new programs to detect and mitigate adverse drug reactions and enhance drug safety. Section 921 of FDAAA amends the Federal Food, Drug, and Cosmetic Act (FD&C Act) to require FDA to submit a report to Congress regarding internal procedures and processes for addressing ongoing postmarket safety issues identified by OSE and how recommendations of OSE are handled within the Agency.

The following report has been prepared to meet this requirement. The report summarizes procedures and processes that FDA has developed and implemented since the passage of FDAAA that collectively aim to improve the working relationship between the offices responsible for reviewing and approving drugs and the office responsible for monitoring safety during the postmarket period.

CDER has adopted a uniform approach for addressing ongoing postmarket safety issues whether a safety issue is identified by OSE, OND, or any other office in CDER. Continued collaborative efforts are ongoing to develop and refine principles and processes to more effectively incorporate OSE's experience and expertise into the overall management of drug safety.

II. Background

In September 2006 the Institute of Medicine (IOM) issued a report on its assessment of the U.S. drug safety system, "*The Future of Drug Safety – Promoting and Protecting the Health of the Public.*"² The report makes substantive recommendations on how FDA could improve risk assessment, surveillance, and the safe use of drugs, including actions other parts of government should take to create a more robust and comprehensive system for better ensuring the safe use of medical products.

One provision of FDAAA directed the Secretary of Health and Human Services to issue a report that would address FDA's plan for responding to the IOM recommendations. Section III. C. of *FDA's Response to the Institute of Medicine's 2006 Report*³ addressed the recognized need to sharpen the focus on the culture of drug safety in CDER, to promote mutual respect between pre-approval and post-approval staff and to clarify roles and responsibilities. FDA initiated actions aimed to engender improved integration of

¹ Pub. Law 110-85, September 27, 2007.

² Full report available for purchase at <http://www.iom.edu/Reports/2006/The-Future-of-Drug-Safety-Promoting-and-Protecting-the-Health-of-the-Public.aspx>. The report may be read online for free at http://books.nap.edu/openbook.php?record_id=11750

³ <http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM171627.pdf>

drug safety into regulatory decision-making throughout the drug review cycle, including improved means for managing scientific disagreements. In the four years since FDA issued its response to the IOM report, important changes have taken place in CDER to improve the working relationship between OSE and OND, in particular, as well as between OSE and other offices throughout CDER.

CDER has put into practice a team-based approach for the review of postmarket drug safety issues that engages staff from OND and OSE, as well as other offices throughout the Center. CDER uses this team-based approach for all drug safety issues, regardless of how or in what office the safety issue is first identified.

The new procedures and processes described in this report operationalize CDER's commitment to assuring that OSE's expertise and areas of responsibility are fully integrated within the Center in an environment favorable to comprehensive, ongoing safety surveillance of marketed drug products.

III. Programs and Procedures Established Since the Passage of FDAAA

Since the passage of FDAAA, CDER has developed and added several new policies and procedures to its Manual of Policies and Procedures (MAPP); each of these MAPPs are further detailed in this report. CDER is applying the new authorities to address postmarket drug safety issues and to meet the required new postmarket safety requirements under the statute. In addition, CDER developed a number of complementary MAPPs⁴ to fulfill the objectives of the overarching Safety First Initiative (Safety First), described in section III. A.

A. Safety First Initiative

FDA has built a framework for integrating postmarket drug safety activities – the Safety First Initiative and the Safe Use Initiative. The mission of *Safety First* is to strengthen and modernize CDER's *internal* safety-related policies and procedures to manage significant safety issues. The parallel mission of *Safe Use* is to partner with the *health care system* to ensure that medicines are used safely and appropriately. The *Safe Use*⁵ initiative has an external focus, thus its programs are not covered in this report.

CDER's Safety First Initiative has the following specific objectives:

- create and maintain a collaborative, multidisciplinary, team-based approach to the review of drug safety;
- apply world-class project management to ensure FDA focuses the same attention on postmarket drug safety issues as it does on its premarket review;
- align policies and processes to ensure that the most appropriate and best-qualified experts lead and have an equal voice in regulatory decisions;

⁴ CDER MAPPs may be found at <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/default.htm>

⁵ <http://www.fda.gov/downloads/Drugs/DrugSafety/UCM188961.pdf>

- build the scientific, administrative, and technological capacity to carry out the provisions of FDAAA and the Prescription Drug User Fee Act; and
- ensure that significant postmarket drug safety issues are our highest priority.

1. Safety First Steering Committee

The Safety First Steering Committee (SFSC) was formed to direct and oversee activities taking place under the Safety First Initiative. The SFSC has as its stated mission “to put into place the policies, procedures, practices, and technology needed to fulfill CDER’s enhanced mission of ensuring safety throughout the drug lifecycle by giving premarket drug review and postmarket safety an equal focus.” The SFSC is focused on improving oversight and accountability for managing postmarket safety issues by establishing criteria for safety issue prioritization and instituting safety issue management timelines. The SFSC is formalizing the factors that determine what drug safety issues are referred to external groups, such as advisory committees or FDA’s Drug Safety Oversight Board, for advice. The SFSC has also initiated an update to the guidance on drug safety communication (*Drug Safety Information — Food and Drug Administration’s Communication to the Public*)⁶.

2. Safety First Implementation Team

The SFSC established the Safety First Implementation Team (SFIT) to both raise awareness about and enhance understanding of Safety First, as well as establish new procedures and practices to address safety issues across CDER. OSE staff are active members of the SFIT and continue to participate in developing and implementing new MAPPs to address the regulatory authorities brought about by FDAAA, as well as provide outreach and training to all CDER staff. These efforts have led to the successful implementation of the new processes directed at ensuring drug safety throughout the product lifecycle.

B. Memorandum of Agreement Between the Office of New Drugs and the Office of Surveillance and Epidemiology

On June 16, 2008, CDER established a memorandum of agreement (MOA) between OND and OSE to document CDER’s commitment to the timely resolution of drug safety issues and to affirm CDER’s collaborative and multidisciplinary approach to the review of drug safety over the course of a drug’s life cycle. While the two offices worked under the agreement over a two-year period, they developed and put in place several MAPPs to operationalize the principles established in the MOA, many of which are described in the sections below. Because the new MAPPs (4151.7R; 6700.4; 6010.9; 4151.1; 4151.2; 4151.8; 6720.2; 6010.9) document and formalize the principles initially laid out in the agreement, the MOA has not required renewal and is now obsolete.

⁶<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072281.pdf>

C. Joint Safety Meetings Between the Office of New Drugs and the Office of Surveillance and Epidemiology

OND and OSE share responsibility for the review of postmarket safety information for drugs and therapeutic biologics. Because of the joint nature of these responsibilities, OND and OSE concurred that there is a fundamental need for regularly scheduled interactions to exchange information. Prior to the passage of FDAAA, many OND review divisions and the OSE staff assigned to monitor those divisions' drug groups were meeting regularly to share information about emerging issues, develop strategies to identify and analyze safety signals, coordinate their activities, and share decision making about next steps on specific issues. However, such meetings were not uniform across the Center and were not conducted in a uniform manner.

Since early 2009, OSE and OND staff have been operating under a new CDER MAPP⁷ that addresses the roles and responsibilities of OND and OSE regarding the joint meetings, establishes the recommended meeting frequency, and defines the meeting participants, including staff from other CDER offices. The implementation of the new MAPP has resulted in more consistency in these important cooperative meetings.

D. Use of the Document Archiving, Reporting and Regulatory Tracking System for Significant Safety Issues

The Document Archiving, Reporting and Regulatory Tracking System (DARRTS) is an electronic workflow tracking and information management system that maintains official submission records and has the capability to track all communications and documentation concerning these submissions. The DARRTS platform includes a specific functionality, the Tracked Safety Issue (TSI), for managing and archiving significant postmarket safety issues. CDER developed a MAPP⁸ to outline the roles, responsibilities, and procedures for staff in OSE, OND, and other CDER offices for managing significant safety issues related to marketed drug products. The tracking system allows for significant safety issues to be initially identified and entered into the system by staff in either OSE or OND.

⁷ MAPP 4151.7R -- Joint Safety Meetings Between OND and OSE -- Issued 3/26/2009

⁸ MAPP 6700.4 -- Tracking of Significant Safety Issues in Marketed Drugs -- Use of the DARRTS Tracked Safety Issue -- Issued 6/8/2009

E. Establishing and Operating Safety Issue Teams in the Center for Drug Evaluation and Research

Following the passage of FDAAA, CDER established new processes and procedures to enable use of multidisciplinary review teams to review and manage postmarket safety issues. Staff from OND and OSE are the primary members of safety issue teams, with staff from other CDER offices included as appropriate, depending on the safety issue. An interim MAPP lays out the steps involved in managing these safety issues. Once an issue is identified, it is entered into DARRTS (see above). A safety issue team then meets to plan the review components and processes. The team determines what data are necessary, and whether discussions by internal advisory bodies (such as the Drug Safety Oversight Board), regulatory briefings, or meetings of external bodies, such as advisory committees, are warranted for each particular safety issue. Decisions on specific actions to take are then documented and entered into the tracking system, allowing CDER to continuously monitor and track an issue. CDER uses established processes to inform applicants about safety concerns and to carry out public communications and, where necessary, compliance actions. CDER continues to work on refining how the multidisciplinary teams work together to manage these ongoing significant safety issues.

F. New CDER Policies and Procedures on Dispute Resolution, Resolution of Differing Professional Opinions, and Equal Voice

On October 16, 2010, CDER issued three new and related MAPPs to 1) provide guidance to staff on documenting differences of opinion, 2) describe policies involved in the panel review of differing professional opinions, and 3) foster a collaborative environment for decision-making.

The first MAPP, *Scientific / Regulatory Dispute Resolution for Individuals Within a Management Chain*,⁹ provides the policies and procedures that CDER staff within a management chain, such as an office or discipline, are to follow in resolving differences of opinion on scientific or regulatory matters. It conveys to individuals who are initiating or involved in the dispute resolution process a set of guidelines for documenting scientific and regulatory review findings, perspectives, and opinions.

A companion directive,¹⁰ *Resolution of Differing Professional Opinions: Review by Ad Hoc Panel and CDER Director*, sets forth the policies, responsibilities, and procedures to be used by CDER staff to express Differing Professional Opinions (DPOs). These concern regulatory actions or policy decisions with significant public health impact in instances when normal procedures for resolving internal disputes are not sufficient. So that such disputes may be resolved expeditiously, the DPO procedure provides short time frames for the panel to review and consider the DPO.

⁹ CDER MAPP 4151.1 Revision 1, *Scientific/Regulatory Dispute Resolution for Individuals Within a Management Chain*, Effective 9/16/10.

¹⁰ CDER MAPP 4151.2, Revision 1, *Resolution of Differing Professional Opinions: Review by Ad Hoc Panel and CDER Director*, Effective 09/16/10.

It also specifies that the DPO be reviewed by qualified staff who are not directly involved in the decision under consideration. The policy directs all in the supervisory and management chain to support the DPO process and to protect employees from even the appearance of retaliation for having a differing viewpoint and using the DPO process. The MAPP designates the CDER Ombudsman as the focal point for receiving, managing, and facilitating the DPO process.

A third CDER policy directive,¹¹ *Equal Voice: Discipline and Organizational Component Collaboration in Scientific and/or Regulatory Decisions* (Equal Voice or EV), provides general guidance to staff for incorporating the philosophy and practices of Equal Voice into CDER decision-making processes. CDER developed the EV initiative to ensure that, regardless of where the signatory authority resides, CDER makes decisions only after it brings all appropriate expertise to bear.

EV expands on existing policies and procedures and requires a collaborative environment for decision-making. Such an environment requires open communication and exchange of ideas in a mutually respectful professional environment, and the full and open participation of all relevant disciplines and organizational components in the decision-making process. CDER expects that the EV process will increase engagement and transparency and allow early identification of concerns that could disrupt the decision-making process.

Another major CDER initiative, the Workplace Culture Initiative, instills guiding principles of communication, collaboration, community, conflict management, and consumer focus (the “5 Cs”) in CDER processes. EV provides a foundation to achieve the 5 Cs in the way CDER conducts its business and thereby contributes to excellence in decision-making across the Center.

G. Premarket Safety Review

1. Integration of OSE into the 21st Century Review Process

In 2007, CDER initiated the 21st Century Review Process, a comprehensive set of procedures and timelines for the team-based review of new drug applications (NDAs) and biologic license applications (BLAs). Using this new approach, representatives from various disciplines and offices work with team leaders and project managers, using a quality systems approach to conduct reviews of original applications.

The 21st Century Review Process covers all relevant steps in the review process, from the NDA or BLA review planning stage to the post-action feedback meeting. Since the launch of this new process, CDER has made ongoing improvements to streamline handoffs between the expanded core review team and other participants, and CDER has developed a set of supportive tools and training.

¹¹ MAPP 4151.8 – Equal Voice: Discipline and Organizational Component Collaboration in Scientific and/or Regulatory Decisions – Issued 9/16/10

In the past, OSE's work, which is focused on managing postmarket safety issues, was not routinely included in this process, largely because OSE's traditional role was focused on activities occurring after drug approval. More recently, OSE's roles and responsibilities have been formally integrated into the full pre-approval review process — while the application is still under review.

OSE's role is outlined in the CDER 21st Century Review Process Desk Reference Guide¹², which describes how OSE should be involved from the beginning of the review, particularly if the application contains postmarketing safety activities. The Guide also stipulates that OSE should be consulted whenever an important safety concern has been identified that requires postmarketing activities or additional OSE expertise. OSE's review team members are to be included in any meetings relevant to their discipline involvement; for example, OSE epidemiologists attend meetings where CDER discusses postmarket requirements for observational epidemiologic studies.

2. Proprietary Name Review

OSE's Division of Medication Error Prevention and Analysis (DMEPA) is involved in a number of initiatives to prevent events that may cause or lead to inappropriate medication use or patient harm. DMEPA provides pre-marketing reviews of all proprietary names, labels, and labeling in CDER to reduce the medication error potential of a proposed product. In April 2009, DMEPA was granted signatory authority for all decisional letters regarding review of proprietary names. In response to this new DMEPA authority, CDER developed a MAPP¹³ to describe procedures to be used by the several CDER offices involved in handling requests for proprietary name review that may be submitted to investigational new drug applications (INDs), NDAs, BLAs, efficacy supplements, or labeling supplements.

3. Review of Risk Evaluation and Mitigation Strategies (REMS)

FDAAA created a new section (505-1) of the FD&C Act that authorizes FDA to require applicants to submit a proposed REMS if the FDA determines that a REMS is necessary to ensure that the benefits of a drug outweigh its risks. OND, OSE, the Office of Compliance, and CDER's Division of Drug Marketing, Advertising, and Communications (DDMAC) collaborate in this effort.

4. Postmarket Requirements and Commitments

The phrase *postmarket requirements and commitments* refers to studies and clinical trials that sponsors conduct after approval to gather additional information about a product's safety, efficacy, or optimal use.

¹²<http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/UCM218757.pdf>

¹³ MAPP 6720.2 -- Procedures for Handling Requests for Proprietary Name Review

Section 505-1 of the FD&C Act authorizes FDA to require applicants to conduct postapproval studies or clinical trials to assess known serious risks, to assess signals of serious risks, or to identify unexpected serious risks when the potential for such has been identified.

A CDER MAPP,¹⁴ issued in March 2009 and updated in April 2010, defines postmarket requirements and commitments and describes the policies and procedures to be used by CDER staff to develop them. A Postmarket Requirement (PMR) is any study or clinical trial that an applicant is required to conduct after approval of a marketing or licensing application or a supplement. A Postmarket Commitment (PMC) is any study or clinical trial that an applicant has agreed, in writing, to conduct after approval of a marketing or licensing application or supplement that is not a PMR.

The above cited MAPP provides documentation of the PMR/PMC processes, roles, and responsibilities that span the period from first identification of an issue during a premarket safety review of an NDA or BLA, to the time the PMR/PMC is finalized. These processes involve reviewers, project management staff, and senior management in OSE and throughout CDER.

H. Postmarket Safety Review

1. Postmarket Drug Safety Evaluation Summaries

Section 915 of FDAAA (505(r)(2)(D) of the FD&C Act), requires FDA to prepare, by 18 months after approval of a drug or after use of the drug by 10,000 individuals, whichever is later, a summary analysis of the adverse drug reaction reports received for the drug, including identification of any new risks not previously identified, potential new risks, or known risks reported in unusual number. These evaluations are done to determine if there are any new serious adverse events not previously identified during product development, known side effects reported in unusual number, or potential new safety concerns observed after products are used in the general population. Scientific reviewers from CDER's OSE and OND collaboratively review relevant data, summarize their findings and, when necessary, develop a plan to further investigate potential new safety issues.

2. Risk Evaluation and Mitigation Strategies (REMS)

The review of REMS in the pre-approval period is described in section G. 3. Section 505-1 of the FD&C Act also authorizes FDA to require holders of covered applications approved without a REMS to submit a proposed REMS if the FDA becomes aware of new safety information as defined in section 505-1(b)(3) of the FD&C Act and determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks of the drug. The review team, with representatives from OND, OSE,

¹⁴ MAPP 6010.9 -- Procedures and Responsibilities for Developing Postmarketing Requirements and Commitments -- Issued 3/10/2009; updated 4/26/2010

the Office of Compliance, and CDER's Division of Drug Marketing, Advertising, and Communications (DDMAC), all work together to perform a collaborative review.

In addition to reviewing proposed REMS submissions, OSE and OND staff review assessments of REMS submitted by industry. Based on these assessments and other information, staff may determine that a REMS needs to be modified to ensure that the benefits of a drug outweigh its risks.

3. Postmarket Requirement Studies

As described in section G. 4., section 505-1 of the FD&C Act authorizes FDA to require applicants to conduct postapproval studies or clinical trials. In the postmarket period, the same requirements may be made, for the same purposes as during the premarket period, but with the distinction that the requirement be based upon new safety information.

Postmarket requirements may involve pharmacoepidemiologic and/or observational studies, and OSE epidemiologists play a key role in their design and review.

4. Safety Labeling Changes

Section 901 of FDAAA amended the FD&C Act to authorize FDA to require application holders of approved drugs and biological products to make safety labeling changes based on new safety information that becomes available after approval of the drug or biological product. The decision regarding whether to require safety labeling changes may necessitate discussions among multiple CDER offices. OSE collaborates with OND and other offices to discuss the new safety information and determine whether safety labeling changes should be required.

I. Epidemiology

The Pharmacoepidemiology Research Program was established to advance scientific collaborations between FDA and multiple pharmacoepidemiologic experts who have access to extensive healthcare data resources, and provides for the initiation and completion of pharmacoepidemiologic safety studies. OSE, OND, and external epidemiology research investigators work together on study teams to complete in-depth safety studies, the results of which serve to both inform FDA's regulatory decision making process and enhance drug safety assessments.

In February 2011, FDA issued a draft guidance *Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets*.¹⁵ It includes recommendations to industry for submitting pharmacoepidemiologic safety study protocols and reports to FDA that contain sufficient information on their design, analysis, and results to permit thorough review by FDA staff. In addition, the draft guidance provides a framework for FDA reviewers to use when reviewing and interpreting

¹⁵<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM243537.pdf>

these submissions, as well as consistent guidance for FDA to use when conducting these studies.

J. Sentinel Initiative

In May 2008, the U.S. Department of Health and Human Services (DHHS) and FDA announced the launch of FDA's Sentinel Initiative, a long-term program designed to build and implement a national electronic system for monitoring the safety of FDA-approved drugs and other medical products. Once completed, the system under development by the Sentinel Initiative will be called the Sentinel System.

Section 905 of FDAAA directs FDA to develop enhanced capacities for monitoring drug safety after approved products reach the market. Using a scientific approach called "active surveillance," the Sentinel Initiative is designed to ensure that the Sentinel System will fulfill the mandates included in FDAAA.

The Sentinel System will augment FDA's existing postmarket safety monitoring systems, which currently rely on external sources to report suspected medical product-related adverse reactions (a form of safety monitoring known as "passive surveillance"). In contrast, the Sentinel System will be an "active surveillance" system, enabling the Agency to initiate its own internal safety evaluations that use available electronic healthcare data to investigate the safety of medical products.

CDER's Office of Medical Policy (OMP) leads the FDA-wide development of the Sentinel System tools and resources and coordinates efforts related to the Sentinel Initiative across the centers. OSE leads the CDER-wide implementation of these capabilities and is spearheading efforts to develop policies, processes, and procedures that will govern how CDER will use the system. With the creation of the Sentinel System, various CDER offices will be able to submit safety signals for evaluation. OSE has created a CDER-wide Sentinel Steering Committee that will deal with procedures, priorities, and policies related to CDER's use of the Sentinel System. This committee will address the procedures involved with submitting and prioritizing drug related safety queries, as well as guidelines for reviewing results in the context of what is already known about a given safety signal from other information sources.

K. Communicating Safety Issues to the Public

1. Quarterly Postings of Safety Issues Identified from the AERS Database

Section 921 in FDAAA directs FDA to, among other things, post a quarterly report on the Adverse Event Reporting System (AERS) Web site¹⁶ of any new safety information or potential signal of a serious risk identified by AERS within the last quarter. Staff from CDER and the Center for Biologics Evaluation and Research (CBER) regularly examine the AERS database as part of routine safety monitoring. Any potential signal of a serious

¹⁶<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm082196.htm>

risk is entered as a safety issue into DARRTS or into CBER's Therapeutics and Blood Safety Branch Safety Signal Tracking system. The information in each quarterly section 921 posting, including the names of products and potential safety issues, is derived from these two systems. A MAPP issued on March 29, 2011,¹⁷ defines the policies and procedures for the quarterly postings.

2. Drug Safety Communications

In January 2010, CDER began issuing a single type of communication to provide the public with easy access to important postmarket drug safety information. The new Drug Safety Communication replaces the previous communications used by CDER to disseminate drug safety information (Early Communications, Follow-Up Early Communications, Information for Healthcare Professional sheets, and Public Health Advisories). The Drug Safety Communications are written in an interactive messaging format that allows the public to access information most relevant to them.

3. Postmarketing Drug Safety Evaluations

Section H.1. describes the FDAAA requirement for FDA to prepare Postmarket Drug Safety Evaluation Summaries. FDA has created an FDA public Web site that provides summary information about ongoing and completed postmarket safety evaluations of adverse drug experience reports made to FDA for NDAs and BLAs approved since September 27, 2007.¹⁸ The Web site includes a table that lists the subject products by name, application number, approval date, approved indication, summary of evaluation findings, actions taken, and ongoing surveillance activities.

4. Postmarket Drug Safety Information Web Site

CDER recently launched a Web site for patients and providers, offering multiple links to postmarket drug safety information.¹⁹ This Web site includes sections on and multiple links to clinical studies of approved products, recent safety information, information about FDA's Drug Safety Oversight Board, general health information, and information about drug labeling, REMS, and regulations and guidance documents.

IV. Conclusions

Working to ensure the safety and effectiveness of drugs regulated by FDA has always been a critical component of the Agency's mission to protect and promote the public health. This report highlights CDER's commitment to assure that OSE's expertise and areas of responsibility are fully integrated into CDER processes in an environment

¹⁷ MAPP 6700.9 -- FDA Posting of Potential Signals of Serious Risks Identified by the Adverse Event Reporting System – Issued 3/29/2011

¹⁸ http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/ucm204091.htm#Postmarketing_Summaries

¹⁹ <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/default.htm>

favorable to ensuring the safety of marketed drug products. CDER has invested substantial resources to ensure that postmarket safety issues identified by OSE, or any other office in CDER, are collaboratively managed. This report has highlighted the many CDER activities underway to refine existing processes and develop new policies and procedures for safety issue identification, assessment, and decision-making.