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DRUG SAFETY: IT'S A LEARNING PROCESS

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INTRODUCTION

The Food and Drug Administration (FDA) approved every drug currently on the market after successfully completing a complex multi-stage review and approval process.¹ Beginning an investigational new drug application (IND), a drug must complete three phases of clinical trials.² Phase I studies assess how the human body metabolizes low doses of the drug and the resulting side effects.³ Phase II measures the efficacy and safety of the drug in a small number of patients who suffer from the targeted illness or condition.⁴ In Phase III, drug sponsors must provide FDA with substantial evidence confirming their successful Phase II results

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¹ See Sean M. Basquill, Comment, *Prescription Drug Liability and Postmarketing Surveillance: A Modest Proposal*, 25 TEMP. J. SCI. TECH. & ENVTL. L. 69, 74 (2006) (explaining the purpose of maintaining a strict evaluation process and the necessity of a multi step review system); see also FDA, About the Food and Drug Administration, http://www.fda.gov/cder/info/consumer_approved.htm (last visited Aug. 1, 2008) [hereinafter About the Food and Drug Administration] (discussing the steps in the review process for the approval of a new drug).

² See 21 C.F.R. § 312.20 (2008) (stating the requirements for an IND); see also Charles Steenburg, *The Food and Drug Administration's Use of Postmarketing (Phase IV) Study Requirements: Exception to the Rule?*, 61 FOOD & DRUG L.J. 295, 296 (2006) (discussing the three phase process to obtaining approval for a drug after passing the preliminary safety tests).

³ See 21 C.F.R. § 312.21(a) (2008) (stating the phase one requirements for approval of an IND). See generally Steenburg, *supra* note 2, at 296 (discussing the origin of the multi-stage review and explaining the three requisite phases).

⁴ See 21 C.F.R. § 312.21(b) (2008) ("Phase 2 includes the controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study . . ."); see also Steenburg, *supra* note 2, at 296 ("Phase II trials evaluate both efficacy and safety in a small number of patients who actually suffer from the ailment that the investigational drug targets.").

⁵ See 21 C.F.R. § 312.21(c) (2008) ("Phase 3 studies are expanded controlled and uncontrolled trials. They are performed after preliminary evidence suggesting effectiveness of the drug has been obtained . . ."); see also Steenburg, *supra* note 2, at 297 ("Phase III studies are significantly larger investigations that seek to confirm the results of successful Phase II trials . . .").

⁶ See Steenburg, *supra* note 2, at 296-97 (discussing the steps for approving the drug for marketing after the three phases); see also About the Food and Drug Administration, *supra* note 1 (stating that new drugs which successfully complete the approval process may be marketed with the consent of the FDA).

with a significantly larger patient-base.⁵ After Phase III, the FDA may make a determination allowing the drug to be marketed.⁶

But what happens to the drug after approval? Despite the rigorous testing and monitoring that occurs pre-approval, the most serious adverse effects arise after the drug is made available to the general population.⁷ Therefore, postmarketing surveillance should be treated as an essential follow-up to the approval process.⁸ The FDA's current postmarketing regulation consists of Phase IV study commitments, and an adverse events reporting system (AERS).⁹ Postmarketing commitments are aimed at ensuring a drug's safety after approval,¹⁰ while the purpose of AERS is to detect patterns of actual or potential adverse events.¹¹ However, this postmarketing surveillance system is far from perfect.¹² Regardless of its status as the world's leading pharmaceutical regulatory agency,¹³ the FDA

⁷ See Stephen J. Schanz, *Pharmaceutical Postmarket Review: Fact or Fiction?*, 62 FOOD & DRUG L.J. 493, 493 (2007) (discussing the necessity for strong controls and monitoring of new drugs after they have been cleared for marketing); see also David A. Kessler & David C. Vladeck, *Health Regulation and Governance: A Critical Examination of the FDA's Efforts to Preempt Failure-to-Warn Claims*, 96 GEO. L.J. 461, 490 (2008) (remarking on the shortcomings of the post marketing monitoring process of newly approved FDA drugs).

⁸ See Schanz, *supra* note 7, at 495 (contending that "postmarket surveillance is an important adjunct to the approval process which cannot be ignored"); see also Steenburg, *supra* note 2, at 298 (considering former FDA Commissioner George Larrick's testimony that the "early period following general marketing of a drug may be regarded as a final step in the testing of a product" (quoting *Drug Safety (Part One): Hearings Before a Subcomm. of the H. Comm. on Government Operations*, 88th Cong. 152 (1964) (statement of George P. Larrick, Commissioner, Food and Drug Administration))).

⁹ See Schanz, *supra* note 7, at 494 (highlighting the importance of the two components); see also Kessler & Vladeck, *supra* note 7, at 489 (discussing the steps in the post approval monitoring process of the drug).

¹⁰ See Schanz, *supra* note 7, at 494 ("The objective in carrying out and evaluating these trials is to determine how safe and effective the drug is and whether it qualifies for market approval."); see also Kessler & Vladeck, *supra* note 7, at 489 ("[T]he FDA [has] authority to require Phase IV studies for drugs already approved if the FDA makes a determination that 'new safety information' shows an unexpected risk that cannot be addressed through other controls.").

¹¹ See Rosalie A. Bright, *Strategy for Surveillance of Adverse Drug Events*, 62 FOOD & DRUG L.J. 605, 605 (2007) ("The main goal of drug surveillance is to obtain warnings of previously unidentified adverse drug events (ADE) and to detect patterns of actual or potential ADE."); see also Lance L. Shea et al., *Cause and Effect? Assessing Postmarketing Safety Studies as Evidence of Causation in Products Liability Cases*, 62 FOOD & DRUG L.J. 445, 446-47 (2007) ("[A]dverse event reports are helpful in directing further inquiry by detecting possible signals of unusual adverse events or unusual numbers of common adverse events.").

¹² See Katharine Neckers, *Harmonization of Drug and Medical Device Development in the US and Japan: Movement Towards International Cooperation in the Postgenomic Era*, 12 NEW ENG. J. INT'L & COMP. L. 295, 302 (2006) (characterizing and listing a majority of the current shortcomings within the current surveillance system); see also Bert Black & Keith Altman, *Deciphering the Adverse Event Reporting System*, 41 TRIAL 36, 40 (2005) (acknowledging that the voluntary nature of the AERS and unstandardized criteria that doctors use in determining whether an adverse reaction should be reported can make the quality of AERS reports uneven).

¹³ See Steenburg, *supra* note 2, at 299 (tagging the FDA as the "world's first regulator to decide whether to send a given drug out into commerce"); see also Lars Noah, *One Decade of Food and Drug*

may stand to learn from its two main competitors: the European Union (EU) and Japan.¹⁴ Both the EU and Japan consider postmarket monitoring of drugs as a top priority; each taking strong measures to ensure drug safety.¹⁵ The EU's "pharmacovigilance" system threatens liability if certain postmarketing regulations are not complied with.¹⁶ Japan targets the early stages in postmarketing surveillance and requires early adverse reaction reports, as well as early clinical investigations and studies.¹⁷ With the FDA's problems of enforcing compliance from pharmaceutical companies' underreporting of adverse events and overall monitoring,¹⁸ postmarketing surveillance in the U.S. would greatly improve if the FDA emulated certain aspects of the EU and Japanese postmarketing surveillance systems.

Part I of this note will provide background on the FDA's statutory authority. It will outline the Food and Drug Administration Modernization Act of 1997,¹⁹ and the authority that the FDA derives from it. This section will focus on the two key aspects of postmarket pharmaceutical regulation – postmarketing study commitments and adverse event reporting, and their

Law Scholarship: A Selected Bibliography, 55 FOOD & DRUG L.J. 641, 641 (2000) (noting that the FDA is a significant regulatory agency because it regulates products that account for 25 percent of consumer expenditures).

¹⁴ See Justina A. Molzon, *The International Conference on Harmonization Common Technical Document – Global Submission Format?*, 60 FOOD & DRUG L.J. 447, 447 (2005) (explaining that in 1990, the United States, Western Europe, and Japan formed the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) mainly because the majority of drugs and medicines were developed in these three regions); see also Rosemarie Kanusky, *Pharmaceutical Harmonization: Standardizing Regulations Among the United States, the European Economic Community, and Japan*, 16 HOUS. J. INT'L L. 665, 676–88 (1994) (detailing the new and extensive processes for regulation of pharmaceuticals and new drug approval in the European and Japanese markets, which make such drugs marketable in the United States).

¹⁵ See discussion *infra* Parts II.A, II.B.

¹⁶ See Duncan Matthews & Caroline Wilson, *Pharmaceutical Regulation in the Single European Market*, 17 MED. & L. 401, 419 (1998) (defining "pharmacovigilance" as the regulatory agencies' ongoing monitoring of safety of pharmaceutical products once they are marketed); cf. Stephen A. Goldman, *U.S. Postmarketing Pharmacovigilance Compliance in the Midst of Regulatory Uncertainty*, 62 FOOD & DRUG L.J. 513, 526 (2007) (suggesting that U.S. pharmaceutical companies would benefit by incorporating the ICH's "pharmacovigilance planning," which went into effect in Europe in November 2005).

¹⁷ See Neckers, *supra* note 12, at 308 (noting that the postmarketing surveillance system in Japan "requires pharmaceutical companies to complete early adverse reaction reports, 'early phase postmarketing vigilance,' clinical experience investigation, special investigations, and postmarketing clinical studies"); see also Rachel F. Ochs, *Pharmaceuticals: The Battle for Control in the 21st Century*, 10 J.L. & HEALTH 297, 331–32 (suggesting that the FDA's stringent regulation of pharmaceutical drugs encourages the Japanese government to improve its clinical testing in order to compete in the American market).

¹⁸ See Neckers, *supra* note 12, at 301–02 (noting that the author does not propose that postmarketing in Japan and the EU is perfect; however, their systems' weaknesses are beyond the scope of this note); see also Peter B. Edelman, *Japanese Product Standards as Non-Tariff Trade Barriers: When Regulatory Policy Becomes a Trade Issue*, 24 STAN. J. INT'L L. 389, 428–29 (1988) (revealing that Japan's regulation of pharmaceuticals has a protectionist effect, causing its pharmaceutical market to operate with a lack of transparency that foreign firms find cumbersome).

¹⁹ Pub. L. No. 105-115, 111 Stat. 2296 (1997).

respective problems. Part II summarizes the regulatory systems in the European Union and Japan, highlighting their unique features. Finally, Part III will propose various changes that should be made to strengthen the FDA's postmarketing surveillance system.

I. POSTMARKETING IN THE U.S.

A. Phase IV

1. Section 130 of the Modernization Act in Effect

The Food and Drug Administration Modernization Act of 1997 requires the FDA to report annually in the Federal Register on the status of postmarketing commitments made by sponsors of drug and biological products.²⁰ Section 506B was added to the Federal Food, Drug and Cosmetic Act, and allowed the FDA to monitor the progress of postmarketing study commitments, which are either voluntarily agreed to, or required.²¹ Under this additional authority, the FDA has promulgated its own rules that provide a framework for the content and format of the annual progress report.²² Published on October 30, 2000, 21 C.F.R. § 314.81(b)(2) modifies annual report requirements for new drug applications (NDAs) and abbreviated new drug applications (ANDAs).²³ Specifically, under section 314.81(b)(2)(vii), applicants of approved drugs must submit annual reports detailing the status of each clinical safety, clinical efficacy,

²⁰ 21 U.S.C. § 356b (2008); Report on the Performance of Drug and Biologics Firms in Conducting Postmarketing Commitment Studies, 72 Fed. Reg. 5069 (Feb. 2, 2007) [hereinafter Report] ("According to the regulations, once a postmarketing study commitment has been made, an applicant must report on the progress of the commitment on the anniversary of the product's approval until the postmarketing study commitment is completed or terminated . . .").

²¹ 21 U.S.C.S. § 356b(a)(1) (explaining that the report must be submitted in a form prescribed by the Secretary in regulations issued by the Secretary); § 130, 111 Stat. at 2331 (noting that any agreement between the Secretary and drug sponsor prior to Act's effective date shall be subject to the requirements of the Act).

²² See Report, *supra* note 20, at 5069 (explaining that section 506B of the Act provides the FDA with authority to monitor the progress of postmarketing studies); 21 C.F.R. § 314.81(b)(2)(vii) (2008) (stating that status reports for pediatric studies shall include statements indicating whether postmarketing clinical studies in pediatric populations were required by FDA under § 201.23).

²³ 21 C.F.R. § 314.81(b)(2) (explaining that applicants shall submit two copies of the report to the FDA division responsible for reviewing the application annually within sixty days of the anniversary date of U.S. approval of the application); see FDA, NEW DRUG APPLICATION (NDA) PROCESS, <http://www.fda.gov/cder/regulatory/applications/NDA.htm> (last visited Aug. 1, 2008) (defining new drug applications as the vehicle through which drug sponsors formally propose that the FDA approves new pharmaceuticals for sale and marketing in the U.S.); see also FDA, Abbreviated New Drug Application (ANDA) Process for Generic Drugs, <http://www.fda.gov/cder/regulatory/applications/ANDA.htm> (last visited Aug. 1, 2008) (identifying ANDA as documents that provide for review and ultimate approval of generic drug products).

clinical pharmacology, and nonclinical toxicology study that is required by the FDA or that they have committed to conduct.²⁴

Once an applicant commits to conducting a postmarketing study, they are required to report annually on the status of the commitment until the study is completed or terminated.²⁵ The FDA may determine that the study has been completed or that it is either no longer feasible or would no longer provide useful information.²⁶ The progress report must include a description of the postmarketing study commitment, a schedule for completing the study commitment, and a characterization of the current status of the commitment.²⁷ A brief explanation of the study's progress is also included.²⁸ A commitment schedule should include projected dates for: (1) submission of the study protocol to FDA, (2) a finalized list of patients, (3) completion of the study, and (4) submission of the final study report to FDA.²⁹ The current status of the commitment must be defined as follows:³⁰ "pending" means the study has not been initiated, but does not meet the criterion for delayed;³¹ "ongoing" indicates the study is proceeding according to or ahead of the original schedule;³² "delayed" signifies that the study is behind the original schedule;³³ "terminated" means the study was ended before completion, but a final study report has not been submitted to FDA; and "submitted" indicates that the study has

²⁴ 21 C.F.R. § 314.81(b)(2)(vii) (discussing that status reports for pediatric studies must include statements indicating whether postmarketing clinical studies in pediatric populations were required by the FDA under § 201.23); *see* Report, *supra* note 20, at 5069 (explaining that postmarketing commitments concerning chemistry, manufacturing, production, controls, and studies conducted on an applicant's own initiative are not required to be reported under §§ 314.81(b)(2)(vii) and 601.70).

²⁵ *See* 21 C.F.R. § 314.81(b)(2)(vii) (noting that the FDA will notify a drug sponsor in writing when study commitment requirements are fulfilled or no longer feasible); *see also* Report, *supra* note 20, at 5069 (stating that applicants must report on progress of reports on anniversary of product's approval).

²⁶ 21 C.F.R. § 314.81(b)(2)(vii) (noting that status of postmarketing studies must be reported annually until provided further determination by the FDA); *See* Report, *supra* note 20, at 5069 (explaining that annual progress reports may be ceased when commitments are no longer required).

²⁷ *See* Report, *supra* note 20, at 5069 (listing three factors central to describing the nature of the study commitment); *see also* FDA, GUIDANCE FOR INDUSTRY: REPORTS ON STATUS OF POSTMARKETING STUDY COMMITMENTS – IMPLEMENTATION OF SECTION 130 OF THE FOOD AND DRUG MODERNIZATION ACT OF 1997 8 (2006) [hereinafter GUIDANCE FOR INDUSTRY], *available at* <http://www.fda.gov/Cber/gdlns/post130.pdf> (highlighting that in most cases the FDA and drug sponsors will have concurred on a protocol before filing the first annual postmarketing study commitment status report).

²⁸ *See* Report, *supra* note 20, at 5069 (explaining that annual report's progress must be detailed in a formal schedule).

²⁹ *Id.* (explaining that four specific dates must be included in the report schedule).

³⁰ *Id.* (listing five definitions that must be provided in an annual report).

³¹ *Id.*

³² *Id.*

³³ *Id.*

been completed or terminated,³⁴ and a final study report has been submitted to FDA.³⁵

The FDA's Center for Drug Evaluation and Research (CDER) is responsible for maintaining the databases of the postmarketing commitment studies reports.³⁶ The progress reports contain information on factors such as: the number of applicants with open (uncompleted) postmarketing commitments, the number of open postmarketing commitments, and the number of open postmarketing commitments for which the FDA did not receive an annual report, etc.³⁷ As required under 21 C.F.R. § 314.81(b)(2)(vii), these reports are available to the public through publication in the Federal Register and on the FDA website.³⁸ The Secretary of Health and Human Services must determine whether a commitment has been satisfactorily completed and, if not completed by the proposed deadlines, why it was not completed.³⁹ If a study is found to have been unsatisfactorily completed, a sponsor may be required to notify practitioners of the failure to complete the studies, including any unanswered questions of safety.⁴⁰

Postmarketing studies can be either required or voluntarily agreed to by sponsors.⁴¹ Agreements by sponsors to voluntarily undertake a

³⁴ *Id.*

³⁵ *Id.*

³⁶ See generally FDA, About the CDER, <http://www.fda.gov/cder/about/default.htm> (last visited Aug. 1, 2008) (describing the organization and functions of the CDER); FDA, REPORT TO CONGRESS: REPORTS ON POSTMARKETING STUDIES (FDAMA 130) 7 (2002) [hereinafter FDAMA 130], available at <http://www.fda.gov/cber/fdama/pstmrktfdama130.pdf> (last visited Aug. 1, 2008) (noting the CDER's procedures for maintaining databases of postmarketing commitments, as well as its development of more efficient systems).

³⁷ See Report, *supra* note 20, at 5069 (listing five details included in every annual report sent to the FDA); FDAMA 130, *supra* note 36, at 8–9 (explaining the specific details that must be reported to the Federal Register); see generally FDA, U.S. FDA CDER Home Page, <http://www.fda.gov/cder/> (providing information on the CDER's history, accomplishments and other general background).

³⁸ See 21 C.F.R. § 314.81(b)(2)(vii) (2008) ("The status of these postmarketing studies shall be reported annually . . . [The] FDA may publicly disclose any information described in . . . this section . . ."); see also Report, *supra* note 20, at 5069 (indicating that disclosed information is also available on the CDER website).

³⁹ See 21 U.S.C. § 356(b)(2) (2008) (providing the requirements a fast track product must meet to receive approval); see also Schanz, *supra* note 7, at 494 (explaining that the Secretary of Health and Human Services is the U.S.'s principle agency in protecting the health of Americans). See generally U.S. Department of Health and Human Services Home Page, <http://www.hhs.gov/about/whatwedo.html> (last visited Mar. 1, 2008) (defining the Secretary's obligations to several public health government agencies).

⁴⁰ See 21 U.S.C. § 356b(e) (2008) ("[T]he Secretary may require that a sponsor who, for reasons not satisfactory to the Secretary, fails to complete by its deadline a study under any of such sections of such type for a drug or biological product . . . notify practitioners who prescribe such drug or biological product of the failure to complete such study . . ."); see also Schanz, *supra* note 7, at 494 (explaining the duties a sponsor may owe to practitioners if their study is found unsatisfactory).

⁴¹ See Schanz, *supra* note 7, at 494. Study commitments are FDA tools to ensure drug safety. *Id.* Together, study commitments and the AE system are a critical stage of the drug approval and

postmarketing study occur either at the time of drug approval, or after approval.⁴² Commitments that are made at the time of drug approval are generally intended to provide additional information about the risks, benefits, and optimal use of the drug.⁴³ Those that are made after drug approval are tailored towards a specific safety concern that has been discovered after approval.⁴⁴

The FDA may require sponsors to conduct postmarketing study commitments only in specific situations.⁴⁵ First, when verification of clinical benefits of drugs that were approved under the accelerated approval process is needed, the FDA has the authority to mandate these postmarketing studies.⁴⁶ Second, if a drug has been approved based only on animal efficacy data, a sponsor must conduct postmarketing studies when ethical and feasible to verify its clinical benefits and safety in humans.⁴⁷ In

monitoring processes. *Id.* The type of regulatory framework determines the effectiveness and safety of a drug. *Id.* “[S]uch [postmarketing] studies are generally not required for most drugs and devices” even though postmarketing studies capture “a critical information production point, because many of the most important safety and efficacy problems only become clear after a drug has entered the patient population.” See Daniel R. Cahoy, *Medical Product Information Incentives and the Transparency Paradox*, 82 IND. L.J. 623, 633 (2007).

⁴² See Schanz, *supra* note 7, at 494 (“[S]ome postmarketing studies can be voluntarily undertaken by sponsors. The agreement to do so can arise at the time the drug is approved or after the FDA grants marketing approval.” (citing GUIDANCE FOR INDUSTRY, *supra* note 27, at 3–4)); see also OFFICE OF THE INSPECTOR GEN., DEP’T OF HEALTH AND HUM. SERVS., FDA’S MONITORING OF POSTMARKETING STUDY COMMITMENTS 3 (2006) [hereinafter HHS OIG], available at <http://oig.hhs.gov/oei/reports/oei-01-04-00390.pdf> (classifying these types of studies as those “requested by FDA and agreed to by drug applicants”).

⁴³ See GUIDANCE FOR INDUSTRY, *supra* note 27, at 4 (stating that most post-approval studies focus on information that is not available upon initial approval); Barbara A. Noah, *Adverse Drug Reactions: Harnessing Experiential Data to Promote Patient Welfare*, 49 CATH. U. L. REV. 449, 457–58 (2000) (highlighting that the pre-approval system provides information about a drug’s efficacy, safety, and side effects).

⁴⁴ See GUIDANCE FOR INDUSTRY, *supra* note 27, at 4 (explaining that most post-approval studies identify problematic results associated with previously approved drugs); Noah, *supra* note 43, at 459–60 (recognizing that post-approval monitoring identifies issues that do not appear during pre-approval studies including: proper dosage, interaction with other drugs, proper use for pediatric and geriatric populations, smoking and alcohol lifestyle habits, and interaction with multiple diseases).

⁴⁵ See Schanz, *supra* note 7, at 494 (listing some of the particular circumstances under which drug sponsors may be required to conduct postmarketing studies); HHS OIG, *supra* note 42, at 1 (stating that the FDA considers postmarketing studies essential in limited circumstances such as accelerated approval applications or mandatory tests for pediatric studies).

⁴⁶ 21 U.S.C.S. § 356b(a)(1) (2008) (“[S]ponsors of a drug that has entered into an agreement . . . to conduct a postmarketing study of a drug shall submit . . . [this report] within 1 year after the approval of such drug”); see 21 C.F.R. § 314.510 (2008) (specifying that the FDA’s marketing accelerated approval for new drugs may be subject to further drug studies); see also FDA, FDA’s Drug Review Process: Ensuring Drugs are Safe and Effective (2002), http://www.fda.gov/fdac/features/2002/402_drug.html (defining accelerated approval as the process that allows an NDA to be approved before conducting normally required measures of effectiveness).

⁴⁷ See 21 C.F.R. § 314.610(b)(1) (2008) (clarifying that approval based on evidence of effectiveness from studies on animals must be augmented by “[t]he applicant . . . conduct[ing] postmarketing studies, such as field studies, to verify and describe the drug’s clinical benefit and to assess its safety when used as indicated when such studies are feasible and ethical”); see also

addition, certain drugs are approved for adults before pediatric studies can be completed.⁴⁸ Therefore, some postmarketing studies are necessary to test the safety and efficacy of the drugs in pediatric populations.⁴⁹ Finally, postmarketing commitments may be mandated when determining whether a previous approval should be revoked.⁵⁰ Another form of postmarketing studies is controls study commitments (CMCs), which are studies that examine the consistency and reliability of a drug's strength, purity, and potency.⁵¹ However, these commitments are not subject to the annual reporting requirement under section 314.81(b)(2)(vii).⁵²

The most recent report in the Federal Register, issued on February 2, 2007, summarizes the status of postmarketing commitments as of September 30, 2006.⁵³ Out of a total of 1,259 postmarketing commitments of NDAs and ANDAs, only 144 were completed.⁵⁴ 899 studies (71 percent)

GUIDANCE FOR INDUSTRY, *supra* note 27, at 3 ("For a drug or biological product approved on the basis of animal efficacy data because human efficacy studies are not ethical or feasible, an applicant must conduct studies when ethical and feasible to verify and describe clinical benefit and to assess the product's safety."); Schanz, *supra* note 7, at 494 (discussing the required postmarketing studies for drugs whose FDA approval depends on animal based data).

⁴⁸ See Pediatric Research Equity Act of 2003, Pub. L. No. 108-155, § 2, 117 Stat. 1936, 1937 (2003) [hereinafter Pediatric Research Equity Act] (authorizing the FDA to require pediatric studies of marketed drugs); see also 21 U.S.C. § 355b(b)(1) (2008) (requiring full investigative reports for drugs that are exclusively pediatric that indicate whether the approved drug is safe and effective).

⁴⁹ 21 U.S.C.S. § 355b(b) (mandating exploratory records to determine an approved pediatric drug's efficacy and suitability); see Pediatric Research Equity Act, *supra* note 48, §§ 2(b)(1)(i)–2(b)(1)(iii) (explaining that marketed drugs and biological products for pediatric populations are subject to post-approval determination of ultimate safety and effectiveness); see also Margaret Gilhooly, *Addressing Potential Drug Risks: The Limits of Testing, Risk Signals, Preemption, and the Drug Reform Legislation*, 59 S.C. L. REV. 347, 368–69 (indicating that the FDA should have increased power to enforce commitments for a post-approval test or surveillance because "failure to complete the [postmarketing] study significantly affects . . . the assessment of the safety of the drug").

⁵⁰ See 21 U.S.C. § 355(k)(1) (establishing that State access to specific clinical records and reports may be necessary for approved drugs); see also GUIDANCE FOR INDUSTRY, *supra* note 27, at 3 (explaining that under 21 C.F.R. § 355(k)(1), "[t]he FDA may also issue an order or regulation requiring an applicant to provide a study report that is necessary and relevant to a determination concerning whether there is or may be grounds for revoking approval of an approved drug"); see also Schanz, *supra* note 7, at 494 (highlighting the statutory standard that requires postmarketing studies to determine whether a drug's approval may be revoked).

⁵¹ See GUIDANCE FOR INDUSTRY, *supra* note 27, at 4 ("[P]ostmarketing CMC studies are conducted because applicants agree, in writing, to conduct such studies to ensure the consistency and reliability of product quality (e.g., strength, purity, and potency)."); see also BIO, THE DIFFERENCE WITH BIOLOGICS: THE SCIENTIFIC, LEGAL, AND REGULATORY CHALLENGES OF ANY FOLLOW-ON BIOLOGICS SCHEME 25 (2007), <http://www.bio.org/healthcare/followonbkg/WhitePaper.pdf> (noting that CMC studies are extremely important to ensuring that a biological product is safe and reliable).

⁵² Compare 21 C.F.R. § 314.81(b)(2)(vii) (2008) ("The status of . . . postmarketing studies shall be reported annually until FDA notifies the applicant, in writing, that the agency concurs with the applicant's determination that the study commitment has been fulfilled or that the study is either no longer feasible or would no longer provide useful information."), with 21 C.F.R. § 314.81(b)(2)(viii) (requiring drug sponsors to annually advise the FDA on the status of CMCs).

⁵³ Report, *supra* note 20, at 5070 (providing a chart that details postmarketing study commitments).

⁵⁴ *Id.*

were pending, 184 (15 percent) were ongoing, 31 (3 percent) were delayed, and 1 (less than 1 percent) study had been terminated.⁵⁵ From these statistics alone, it is evident that these postmarketing study commitments are not being effectively enforced.⁵⁶

2. Problems with Phase IV Postmarketing Commitments

In theory, voluntary commitments by sponsors are an efficient means of collecting postmarketing data.⁵⁷ However, these agreements do not result from “fairly standard negotiating,” thus contributing to the frighteningly low completion rate.⁵⁸ The complex relationship between the FDA and pharmaceutical companies involves political and power struggles, with each side sometimes giving and other times taking.⁵⁹ Under the Prescription Drug User Fee Act (PDUFA) of 1992,⁶⁰ the FDA was authorized to collect fees from companies that produced certain drug and biological products.⁶¹ The PDUFA required that drug manufacturers pay fees to the FDA for the processing of drug applications.⁶² Yet, the PDUFA

⁵⁵ *Id.*

⁵⁶ See Schanz, *supra* note 7, at 495 (“Examining the total umbrella of existing rules, regulations and statutes applicable to drug approval, it must be recognized that the law is not functioning optimally.”); see also HHS OIG, *supra* note 42, at 11–12 (illustrating that during fiscal year 2004, 53 percent of postmarketing study commitments were returned incomplete or with errors).

⁵⁷ See Justin Blum & Jeffrey Tannenbaum, *Drugmakers Fail to do Post-Approval Studies in U.S.*, BLOOMBERG.COM, Mar. 3, 2006, <http://www.bloomberg.com/apps/news?pid=newsarchive&sid=a8BjDILnn2kA> (stating that as many as seventy-five percent of safety studies that drugmakers committed to conduct have not begun); see also Phil B. Fontanarosa, Drummond Rennie, & Catherine D. DeAngelis, *Postmarketing Surveillance – Lack of Vigilance, Lack of Trust*, 292 JAMA 21, (2004) available at <http://jama.ama-assn.org/cgi/content/full/292/21/2647> (suggesting that the lack of completed voluntary study commitments threatens the current system’s ability to ensure drug safety).

⁵⁸ See Steenburg, *supra* note 2, at 333 (“Closer examination raises concerns that many such ‘voluntary agreements’ are nothing of the sort.”); Public Citizen, *FDA Medical Officers Report Falling Standards Permit Dangerous Drug Approvals*, Dec. 2, 1998, <http://www.citizen.org/pressroom/release.cfm?ID=403> (reporting that within the past few years, safety and efficacy standards for approving new drugs have decreased, allowing many drugs that should not have been approved to receive approval).

⁵⁹ See W. John Thomas, *The Vioxx Story: Would it Have Ended Differently in the European Union?*, 32 AM. J.L. & MED. 365, 378 (2006) (criticizing the U.S.’ regulatory process as being too easily influenced by political and economic pressures); see also Chris Joyner, *Source of Rising Drug Costs Disputed*, CHATTANOOGA TIMES FREE PRESS, Mar. 9, 2003, at A8 (suggesting that part of the rising cost of drugs stems from the increasing amounts that pharmaceutical companies are spending on marketing directly to consumers, while spending less on research).

⁶⁰ Pub. L. No. 102-571, § 736(a)(2), 106 Stat. 4491, 4494–95 (2008) [hereinafter “PDUFA”].

⁶¹ See *id.* (noting the companies that produce drugs that are not subject to an exception must pay an annual fee to the FDA Secretary); see also 21 U.S.C. § 379h (2008) (granting the FDA authority to assess and use the enumerated drug fees); Thomas, *supra* note 59, at 372 (using the required fee paid to the FDA to process applications for a drug’s approval is an example of the FDA’s authorization to collect fees). See generally CBER, *Prescription Drug User Fee Act*, <http://www.fda.gov/cber/pdufa.htm> (providing extensive information on the PDUFA).

⁶² 21 U.S.C. § 379h(a)(1)(A) (2008) (stating that every drug applicant must submit a fee to the FDA with the application).

also required the FDA to use the fees to hire employees to review applications faster, creating a problematic system of FDA regulators that were financially dependent upon the same firms they were regulating.⁶³

Moreover, some FDA employees that are responsible for approving drugs have ties to the pharmaceutical companies themselves.⁶⁴ For example, during the highly controversial Vioxx scandal, it was found that ten of the thirty-two FDA advisors whose votes were determinative in allowing Vioxx to return to the market had ties to the drug industry.⁶⁵ Testimony showed that the FDA ignored warnings of increased risk of heart attacks and failed to change the warning label as a result of pressure from drug manufacturers.⁶⁶ A more recent case concerns the morning-after contraceptive pill, which was rejected even before the scientific investigation was completed.⁶⁷ High level FDA management made the premature decision to deny approval of the drug, causing Assistant FDA Commissioner Dr. Susan F. Wood, Director of the Office of Women's Health, to resign, due to the influence of political appointees.⁶⁸ In this way,

⁶³ See Thomas, *supra* note 59, at 372 ("[H]aving the regulators depend financially on the regulated has laid the groundwork for concerns of a system compromised by conflict of interest."); James L. Zelenay, *The Prescription Drug User Fee Act: Is a Faster Food and Drug Administration Always a Better Food and Drug Administration?*, 60 FOOD DRUG L.J. 261, 262 (suggesting that the FDA's dependence on fees from the drug industry creates a glaring conflict of interest).

⁶⁴ Thomas, *supra* note 59, at 377 (noting the ties to the pharmaceutical industry held by FDA advisors involved in approving Vioxx); see Peter Lurie, Cristina M. Almeida, Nicholas Stine, et al., *Financial Conflict of Interest Disclosure and Voting Patterns at Food and Drug Administration Drug Advisory Committee Meetings*, 295 JAMA 1921, 1921 (2006) (reporting that a study of 221 drug-related meetings held by sixteen advisory committees revealed that in seventy-three percent of the meetings, at least one member or voting consultant disclosed a conflict).

⁶⁵ See Thomas, *supra* note 59, at 377 (stating that "ten of the thirty-two FDA advisors on the Vioxx matter had links to the [drug] industry"); see also Carla Sharetto, *FDA 'Too Cozy with Drug Companies,' Senator Charges*, DAILY NEWS CENT., Mar. 12, 2005, <http://health.dailynewscentral.com/content/view/501/62> (reporting charges from Senator Charles Grassley that "[t]he existing Office of New Drugs is hampered by real and perceived conflicts of interest").

⁶⁶ See Thomas, *supra* note 59, at 372-73 (detailing the FDA's refusal to change the warning label on Vioxx packages); Jonathan V. O'Steen & Van O'Steen, *The FDA Defense: Vioxx(R) and the Argument Against Federal Preemption of State Claims for Injuries Resulting From Defective Drugs*, 48 ARIZ. L. REV. 67, 88 (2006) ("Notwithstanding concerns among FDA officials that Vioxx posed significant heart-related risks, the agency sat idly by while Merck spent more than \$100 million annually in direct-to-consumer marketing of Vioxx.").

⁶⁷ See, e.g., Thomas, *supra* note 59, at 377 (commenting that the FDA rejected a morning-after contraceptive pill before finishing its investigation of the drug); see also Julie Rovner, *GAO Questions FDA Decision on 'Morning-After' Pill*, NATIONAL PUBLIC RADIO, Nov. 15, 2005, <http://www.npr.org/templates/story/story.php?storyId=5013111> (describing the General Accountability Office's investigation into the FDA's decision to reject the morning-after contraceptive, Plan B).

⁶⁸ See Thomas, *supra* note 59, at 377 (emphasizing the political override of FDA's advisory panel that had voted twenty-three to four authorizing the sale of the drug); Marc Kaufman, *FDA Official Quits Over Delay on Plan B: Women's Health Chief Says Commissioner's Decision on Contraceptive was Political*, WASH. POST, Sept. 1, 2005, at A8 ("Susan F. Wood, assistant FDA commissioner for women's health and director of the Office of Women's Health, said she was leaving her position after five years because Commissioner Lester M. Crawford's announcement Friday amounted to unwarranted interference in agency decision-making.").

postmarketing studies may be viewed as a combination of FDA personnel bending from external pressures, and higher-level officials wanting to satisfy political agendas.⁶⁹

Another piece of the complicated regulator/regulated relationship is that the FDA effectively has complete discretion in deciding whether to approve a drug.⁷⁰ Although sponsors have a statutory right to appeal FDA decisions rejecting NDAs, courts are unwilling to question the FDA's judgment.⁷¹ Judges are understandably reluctant to approve a drug that FDA experts found to be unsafe.⁷² Furthermore, no effective means exists to prevent the FDA from "sitting" on an application indefinitely.⁷³ Despite the requirement that the FDA take action 180 days after the filing of the application, the FDA has never been forced to do so.⁷⁴ The agency may also act on an NDA by issuing approval letters, but not actually approving the NDA.⁷⁵ For sponsors, the longer the delay in the review process, the more financial losses they will inevitably sustain.⁷⁶ Millions of dollars are

⁶⁹ See Steenburg, *supra* note 2, at 340 (noting that postmarketing studies have become a compromise between external pressures and personal doubts regarding a drug's adequacy); see also Christopher Placitella & Justin Klein, *The Civil Justice System Bridges the Great Divide in Consumer Protection*, 43 DUQ. L. REV. 219, 220–21 (2005) (stating that the FDA appears to be falling under the influence of the industries they are supposed to be regulating and political pressures of the Administration in power).

⁷⁰ See Steenburg, *supra* note 2, at 335 (discussing the FDA's unreviewable discretion to deny approval and ability to prolong the drug review process as evidence that the FDA has virtually complete power); see also Linda Katherine Leibfarth, Note, *Giving the Terminally Ill Their Due (Process): A Case for Expanded Access to Experimental Drugs Through the Political Process*, 61 VAND. L. REV. 1281, 1286–87 (2008) (detailing how the costs, length of time for approval and access to drug testing has effectively given the FDA complete discretion in the drug approval process).

⁷¹ See 21 U.S.C.S. § 355(h) (2008) (granting drug sponsors the right to appeal FDA judgments on NDAs and explaining the procedural steps of an appeal); see also Steenburg, *supra* note 2, at 334 (explaining that although sponsors have the right to appeal, "the agency in practice enjoys complete discretion in deciding whether or not to allow manufacturers to bring their drugs on the market").

⁷² See Steenburg, *supra* note 2, at 335 (stating that judges defer to the FDA experts on questions of drug safety and approval); see also Leibfarth, *supra* note 70 at 1316 (noting that the Supreme Court, recognizing its limitations in the fields of science and medicine, traditionally defers to FDA decisions).

⁷³ Steenburg, *supra* note 2, at 334–35 ("The 1962 . . . FDCA amendments nominally require that FDA take action within 180 days after the . . . filing of an application, but there is no specific enforcement mechanism."); see Charles J. Walsh & Alissa Pyrich, *Rationalizing the Regulation of Prescription Drugs and Medical Devices: Perspectives on Private Certification and Tort Reform*, 48 RUTGERS L. REV. 883, 908–09 (1996) (commenting that the FDA can, effectively, delay review indefinitely by claiming to be unsatisfied with the amount of detail of information provided by the manufacturer).

⁷⁴ See 21 U.S.C.S. § 355(c)(1) (requiring the FDA to take action within 180 days of the application's filing); see also Steenburg, *supra* note 2, at 335 (explaining that there is no specific enforcement mechanism for the 180-day requirement).

⁷⁵ See Steenburg, *supra* note 2, at 335 (stating that approval letters indicate that a drug is effectively approved pending the resolution of certain issues); see also Liora Sukhatme, Note, *Deterring Fraud: Mandatory Disclosure and the FDA Drug Approval Process*, 82 N.Y.U. L. REV. 1210, 1220 (2007) (explaining that the FDA may issue approval letters conditioned on adherence to labeling details and postmarketing requirements).

⁷⁶ See Steenburg, *supra* note 2, at 335 ("With each month that passes without marketing approval,

lost each month a drug remains unapproved.⁷⁷ Consequently, pharmaceutical companies may “agree” to postmarketing commitments in order to speed up the approval process.⁷⁸ The FDA’s power to withhold approval is often characterized as the agency’s “most powerful weapon.”⁷⁹

On the other hand, drug sponsors also have a significant pull over FDA in the area of voluntary commitments.⁸⁰ Sponsors can use media publicity to their advantage by heavily promoting the drug before it is actually approved.⁸¹ If a manufacturer of a promising new drug garners enough support and publicity from the media and the community, “an FDA rejection or delay runs the risk of drawing the ire of legislators and patient advocacy groups.”⁸² For example, the sponsor of the breast cancer drug Arimidex was able to generate enough support from the breast cancer community that it actually informed the FDA that it would not agree to any commitments unless the drug was approved immediately; the FDA obliged in order to avoid any media backlash.⁸³ Also, if the sponsor fails to complete the commitments by the purported deadlines, the FDA may

pharmaceutical and biotechnology firms conceivably lose millions of dollars worth of revenue.”); see also Walsh & Pyrich, *supra* note 73, at 1220 (“Regulatory delay also means that drug manufacturers are not likely to see any immediate returns on their substantial investments in the research development, and . . . approval process.”).

⁷⁷ See, e.g., Mylan Pharms., Inc. v. Shalala, 81 F. Supp. 2d 30, 42 (D.D.C. 2000) (estimating that a drug company could earn approximately \$3 million in revenue between January 10, 2000 and when the FDA planned to grant final approval of its drug on February 9, 2000); Steenburg, *supra* note 2, at 335 (describing how drug sponsors lost revenue while waiting for their drugs to be approved).

⁷⁸ See Steenburg, *supra* note 2, at 336 (explaining that approvable letters offer the FDA a way to exploit leverage, allowing them to pressure sponsors to commit to Phase IV studies in return for getting a straight approval); see also Lars Noah, *U.S. Food and Drug Regulation in Its First Century and Beyond: The Little Agency That Could (Act with Indifference to Constitutional and Statutory Strictures)*, 93 CORNELL L. REV. 901, 913–14 (2008) (noting that many drug companies could not afford to decline accelerated procedures even if it meant submitting to postmarketing restrictions).

⁷⁹ See Steenburg, *supra* note 2, at 336 (quoting a FDA medical officer who characterized “withholding approval as the agency’s ‘most powerful weapon’”); see also George W. Evans & Arnold I. Friede, *The Food and Drug Administration’s Regulation of Prescription Drug Manufacturer Speech: A First Amendment Analysis*, 58 FOOD & DRUG L.J. 365, 389 (2003) (arguing that the FDA’s power to withhold product approval is one of the enforcement weapons in the FDA’s extensive arsenal).

⁸⁰ See Steenburg, *supra* note 2, at 337 (highlighting that drug sponsors are hardly powerless in negotiations with the FDA because such negotiations often occur after the drug is already on the market, a time when the FDA has less leverage); see also Schanz, *supra* note 7, at 494–95 (noting that postmarket negotiations may occur after approval and highlighting that the drug companies and the FDA often have vastly different goals for such projects).

⁸¹ See Steenburg, *supra* note 2 at 338 (claiming that drug sponsors gain a better bargaining position from media attention for their drugs prior to FDA approval); see also Barbara A. Brenner, *The FDA: Promoting Progress or Building Bureaucracy?*, BREAST CANCER ACTION, Mar./Apr. 2003, at 12, <http://bcaction.org/uploads/PDF/76.pdf> (discussing the FDA’s rapid approval of the breast cancer drug Arimidex before it could be fully tested and all side effects known).

⁸² Steenburg, *supra* note 2, at 338.

⁸³ See Steenburg, *supra* note 2, at 338 (mentioning the “major advance publicity” received by some drugs, including Arimidex); see also Brenner, *supra* note 81, at 12 (discussing the great attention devoted by the media to the breast cancer drug Arimidex and its rapid FDA approval).

threaten to withdraw approval of the drug.⁸⁴ However, the threat of withdrawal is almost meaningless.⁸⁵ Drug sponsors are able to “passively” resist completing their studies once they are in place – especially if the drug is already on the market.⁸⁶

According to the Institute of Medicine, many of these studies occur as afterthoughts, late in the review process.⁸⁷ Because these agreements occur at the time of drug approval or after approval, the FDA has limited control in negotiating the details of study protocols to ensure their efficacy.⁸⁸ Conversely, manufacturers also do not have time to assess whether the FDA’s demands are even reasonable, and are deprived of the opportunity to weigh the costs and benefits of the proposed commitments.⁸⁹ Another consequence of deferring these commitments is that many studies are poorly designed, resulting in unnecessary and impracticable tests.⁹⁰

⁸⁴ See 21 U.S.C. § 355(e) (2008) (delineating the FDA Secretary’s ability to withdraw approval of a drug); see also Steenburg, *supra* note 2, at 337–38 (describing circumstances in which the FDA has threatened to withdraw approval).

⁸⁵ See Steenburg, *supra* note 2, at 338 (characterizing the FDA’s threat of withdrawal as “toothless”); see also LARRY D. SASICH ET AL., THE DRUG INDUSTRY’S PERFORMANCE IN FINISHING POSTMARKETING RESEARCH (PHASE IV) STUDIES (2000), available at <http://www.citizen.org/publications/release.cfm?ID=6721> (discussing the rarity of actually withdrawing a drug from market, despite a serious problem); U.S. GOVERNMENT ACCOUNTABILITY OFFICE, DRUG SAFETY IMPROVEMENT NEEDED IN FDA’S POSTMARKET DECISION-MAKING AND OVERSIGHT PROCESS 5 (2006) [hereinafter GAO], available at <http://www.gao.gov/new.items/d06402.pdf> (reporting that most cases of drug withdrawal from the market occur as a result of the sponsor’s actions rather than FDA’s actions); Janis Kelly, *IOM Study Slams FDA, Proposes Top-Down Restructuring and Much More Funding*, MUSCULOSKELETAL REP., Oct. 30, 2006, available at <http://www.mskreport.com/articles.cfm?articleID=1016> (citing that the FDA cannot unilaterally compel companies to fulfill their post marketing study commitments).

⁸⁶ Steenburg, *supra* note 2, at 338 (“[S]ponsors can ‘passively’ resist Phase IV demands”); see Gardiner Harris, *Congressional Investigators Are Critical of F.D.A.’s Efforts to Detect Drug Dangers*, N.Y. TIMES, Apr. 24, 2006, at A12 (discussing the Institute of Medicine’s report which recommends giving the FDA greater authority to force drug makers to complete post-approval clinical trials).

⁸⁷ See Schanz, *supra* note 7, at 495–96. In 2007, the Institute of Medicine (IOM) published “The Future of Drug Safety,” a report that examined FDA’s regulatory oversight. *Id.* Due to recent drug safety problems, many FDA actions have been called into question and IOM was asked by FDA to investigate FDA’s regulatory decision-making and oversight processes. *Id.* Also, Gardner Harris commented that “[t]he report’s conclusions are often damning. It describes the Food and Drug Administration as rife with internal squabbles and hobbled by underfinancing, poor management and outdated regulations.” Gardiner Harris, *Study Condemns F.D.A.’s Handling of Drug Safety*, N.Y. TIMES, Sept. 23, 2006, at A1.

⁸⁸ Steenburg, *supra* note 2, at 337 (citing the FDA’s limited ability to demand post approval study requirements); see Harris, *supra* note 87, at A1 (discussing the Institute of Medicine’s report which criticized the FDA’s regulatory structure and recommended various changes to provide FDA with more regulatory powers in order to better administer the drug approval process).

⁸⁹ See Steenburg, *supra* note 2, at 342 (noting that conferring with drug manufacturers at the last minute denies them the opportunity to assess whether phase IV demands are reasonable); see also Harris, *supra* note 87, at A1 (discussing some of the IOM report’s recommendations for overhauling the FDA’s regulatory system).

⁹⁰ See Schanz, *supra* note 7, at 496 (finding that postmarketing studies implemented late in the review process result in many unfulfilled commitments, ultimately hindering the usefulness of the study); see also Report, *supra* note 20, at 5070 (reporting that twelve percent of total concluded studies

Unnecessary commitment demands made by the FDA waste time and financial resources.⁹¹ Overall, these key factors contribute to the significant number of delayed and incomplete postmarketing studies.⁹²

3. The FDA Lacked an Effective System of Monitoring Postmarketing Commitments

In June 2006, the Office of the Inspector General (OIG) published a report, *FDA's Monitoring of Postmarketing Study Commitments*, evaluating the extent to which the FDA monitors its open postmarketing study commitments.⁹³ After extensive research and interviewing, the OIG concluded that the FDA lacked an effective monitoring system for open commitments.⁹⁴ CDER's Office of New Drugs (OND) employs reviewers who are responsible for checking the accuracy of the annual status reports.⁹⁵ A database is used to help track and monitor the status of the commitments.⁹⁶ In addition to ensuring accuracy, reviewers must also make a determination of the commitment's progress, and how close it is to completion.⁹⁷ Reviewers must indicate whether or not they agree with the

of NDAs and ANDAs are categorized as "no longer needed or feasible").

⁹¹ See Steenburg, *supra* note 2, at 341 ("[U]nnecessary' commitment demands drive up research and development (R&D) costs."); Gilhooly, *supra* note 49, at 368–69 (explaining that drug sponsors with commitments to the FDA are frequently faced with high costs and fears of negative results).

⁹² See Schanz, *supra* note 7, at 496 (stating that communications between the FDA and drug sponsors often occur far into the approval process, impeding the inception or completion of studies); see also Thomas N. Tiedt, *The Drug Safety System Conundrum*, 62 FOOD & DRUG L.J. 547, 554 (2007) (noting that the latest report from the FDA to Congress revealed that two-thirds of postmarketing study commitments were yet to be commenced and just twenty-one percent were ongoing).

⁹³ See HHS OIG, *supra* note 42, at i–ii (describing the OIG's review of FDA's database of postmarketing study commitments from 1990 to 2004 through examination of documents regarding postmarketing study commitments, interviews of CDER project managers, and reviews of FDA policies and procedures regarding postmarketing commitments); Donna Young, *FDA's Monitoring of Postmarketing Studies Probed*, AM. SOC'Y HEALTH-SYS. PHARMACISTS, Aug. 15, 2006, <http://www.ashp.org/import/news/HealthSystemPharmacyNews/newsarticle.aspx?id=2273> (stating that the HHS OIG issued a report discussing the FDA's monitoring of postmarketing study commitments).

⁹⁴ See HHS OIG, *supra* note 42, at 14–16 (detailing problems of FDA postmarketing monitoring system, including difficulty identifying overdue ASRs, a confusing numbering system, and an inconsistently populated database); see also Catherine T. Struve, *The FDA and the Tort System: Postmarketing Surveillance, Compensation, and the Role of Litigation*, 5 YALE J. HEALTH POL'Y L. & ETHICS 587, 662 (2005) ("[T]he FDA's postmarketing surveillance of drugs . . . is less than optimally rigorous. . . . The FDA lacks the resources to adequately analyze postmarketing data and lacks sufficient ability to obtain further information from companies when needed.").

⁹⁵ See HHS OIG, *supra* note 42, at 4–5 (describing reviewers in sixteen CDER review divisions as trained in pharmacy, chemistry, and medicine); see also Kessler & Vladeck, *supra* note 7, at 485 (stating that over 1,000 OND reviewers work on a mere few dozen new drugs every year).

⁹⁶ See HHS OIG, *supra* note 42, at 5 (noting that portions of the database are available on the FDA's website); see also Steenburg, *supra* note 2, at 327 (using the FDA's postmarketing commitment database to show the modest impact accelerated approval regulations have on Phase IV requirements).

⁹⁷ See HHS OIG, *supra* note 42, at 4 ("The main focus of FDA reviews is to validate the accuracy of the information in the ASRs; however, FDA also determines whether drug applicants are making adequate progress towards fulfilling their commitments."); Jill D. Jacobson & David Feigal, *Red Sky in*

proposed status of the commitments and the explanations for that status, which are all offered by the sponsor.⁹⁸ These reports should be reviewed within ninety days of receipt.⁹⁹

The first major challenge in the monitoring system is the fact that FDA officials could not identify which commitments were actually overdue.¹⁰⁰ Many reviewers had to search through a postmarketing commitment database and some even relied on telephone calls from drug applicants themselves to find overdue commitments.¹⁰¹ The OIG also found their database to be outdated, failing to account for many open commitments and drugs that had been withdrawn.¹⁰² A second organizational flaw is the confusing numbering system that is used to categorize commitments.¹⁰³ Numbers that should only be used to indicate a commitment's progress levels are often used for other functions.¹⁰⁴ As a result, many mislabeled commitments are entered into the database, creating confusion for later

the Morning: Modifying Prescription Drug Labels as a Result of Postmarket Surveillance, 62 FOOD & DRUG L.J. 529, 532 (2007) (describing the duty of OND to review various sources of information and make a determination as to what action, if any, is necessary).

⁹⁸ See HHS OIG, *supra* note 42, at 4 (explaining the requirement of reviewers to indicate whether they concur or disagree on the status of commitments and proposed explanations of such status); see also Jacobson & Feigal, *supra* note 97, at 532 (“[OND] is responsible for . . . postmarket monitoring of drug safety, and is the primary decisionmaking authority when it comes to postmarket actions that may be taken with respect to a drug.”).

⁹⁹ See HHS OIG, *supra* note 42, at 4 (describing the FDA's planned review period); see also GUIDANCE FOR INDUSTRY, *supra* note 27, at 14 (providing guidance for applicants to properly submit postmarketing study commitment status reports for approved drugs).

¹⁰⁰ See HHS OIG, *supra* note 42, at 14–15 (noting that reviewers at eight of the fourteen review divisions classified their inability to identify open commitments as a major or moderate challenge in their “ability to effectively monitor the progress” of the commitments); see also FDA, INDEPENDENT EVALUATION OF FDA'S PRESCRIPTION DRUG USER FEE ACT III – EVALUATIONS & INITIATIVES: POSTMARKETING COMMITMENTS STUDY FINAL REPORT 23 (Jan. 2008) [hereinafter INDEPENDENT EVALUATION], available at <http://www.fda.gov/oc/PMC/pmcstudy08.pdf> (commenting on the difficulty in determining which commitments are overdue).

¹⁰¹ See HHS OIG, *supra* note 42, at 14–15 (detailing the steps taken by reviewers to attain the information sought); INDEPENDENT EVALUATION, *supra* note 100, at 23–24 (describing the responsibilities of the reviewers in acquiring the status of postmarketing commitments).

¹⁰² See HHS OIG, *supra* note 42, at 11, 15 (noting that reviewers could not identify a commitment's completion progress and approximately one-third of their annual status reports (ASRs) were either missing or incomplete); see also INDEPENDENT EVALUATION, *supra* note 100, at 23 (presenting evidence of the inefficiency and outdated status of the postmarketing commitment database).

¹⁰³ See HHS OIG, *supra* note 42, at 15 (noting that the FDA database's numbering system for categorizing commitments is confusing); see also FDA, Postmarketing Study Commitments, <http://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm?StartRow=54&StepSize=1&Paging=Yes> (last visited Aug. 7, 2008) (showing evidence, via actual database examples, of the confusing numbering system in the FDA postmarketing database).

¹⁰⁴ See HHS OIG, *supra* note 42, at 15–16 (explaining why the numbering system for categorizing commitments is confusing); see also Press Release, Rep. Edward J. Markey, U.S. Fed News, Rep. Markey Urges FDA to Abide by HHS Inspector General Recommendations on Postmarketing Studies For New Drugs, July 12, 2006 [hereinafter Markey Press Release] (urging the FDA to number commitments uniquely and logically).

reviewers.¹⁰⁵ A third problem is that the FDA database for postmarketing commitments is outdated and lacks useful information.¹⁰⁶ The database rarely includes any information on start dates, projected completion dates, and already completed projects.¹⁰⁷ Without this pertinent data, it is almost impossible to track the status of the commitments, and to determine whether drug applicants are completing their studies on time.¹⁰⁸

More importantly, the OIG found that the surveillance of these commitments was not a high priority for FDA officials.¹⁰⁹ When FDA officials prioritize their workloads, they often do not have the resources and time to fully and effectively monitor postmarketing study commitments.¹¹⁰ As a result of time pressures, reviewers even agreed with drug applicants on terms that were missing from the ASR, thus compromising the accuracy of the reports.¹¹¹ In fiscal year 2004, the FDA only validated thirty percent of the ASRs that were actually submitted.¹¹² Of the ASRs that were validated for accuracy, many of them were not completed within the ninety day period, thus delaying the entire process for FDA and drug

¹⁰⁵ See HHS OIG, *supra* note 42, at 16 (indicating the difficulty that results from mislabeling commitments in the database).

¹⁰⁶ See HHS OIG, *supra* note 42, at 16 (stating that the database does not consistently have the updated pertinent information needed); see also INDEPENDENT EVALUATION, *supra* note 100, at 4 (discussing the outdated and inconsistent nature of the status tracking systems).

¹⁰⁷ See HHS OIG, *supra* note 42, at 16 (giving examples of the incomplete nature of the information compiled in the database); see also Markey Press Release, *supra* note 104 (advising the FDA to include useful time-sensitive information on its database).

¹⁰⁸ See HHS OIG, *supra* note 42, at 16 (noting that without adequate data, it is not possible to readily determine the length of time it takes for applicants to complete their commitments, or whether they are completed at all); see also Neckers, *supra* note 12, at 302 (stating that the lack of information on reports leads to difficulties in determining causal relationships and adverse effects of drugs in postmarket research).

¹⁰⁹ See HHS OIG, *supra* note 42, at 17 (revealing that, according to FDA officials, "reviewing drug applications and documenting FDA/industry meetings are higher priorities than reviewing postmarketing study commitments and ASRs"); see also FDA, FY 2009 Congressional Justification, http://www.fda.gov/oc/oms/ofm/budget/2009/Execsum/1_Exec_Summary.pdf (last visited Aug. 7, 2008) (illustrating the FDA's budget which states that user fees will be increased in 2009 in order to have more resources to review drug applications).

¹¹⁰ See HHS OIG, *supra* note 42, at 17 (reporting that the FDA "lack[ed] the resources to accomplish all of the tasks assigned to them"); see also Basquill, *supra* note 1, at 84-85 (stating that FDA is terribly under-staffed and under-funded).

¹¹¹ See HHS OIG, *supra* note 42, at 18 (revealing that "FDA reviewers sometimes agreed with drug applicants even when the applicants failed to provide one of the status options required by the regulations"); see also Neckers, *supra* note 12, at 302 (stating that the FDA often receives incomplete or inadequate reports).

¹¹² HHS OIG, *supra* note 42, at 17 ("FDA validated only 30 percent (65) of the 217 ASRs that were actually submitted by drug applicants in fiscal year 2004 . . ."); see Pharmaceutical Processing, *FDA Should Fine Companies With Late Post-Marketing Studies*, HHS OIG Says, <http://www.pharmpro.com/ShowPR~PUBCODE~021~ACCT~0000100~ISSUE~0608~RELTYPE~PR~PRODCODE~0000~PRODLETT~O.html> (last visited Sept. 1, 2008) (noting that the FDA is currently training its review division staff on report validation procedures and standardizing the process by which post-marketing study commitments are requested and reviewed in reaction to its low validation numbers).

applicants.¹¹³

Another important finding was that completed ASRs lacked useful information.¹¹⁴ Drug applicants frequently failed to provide information that was required or recommended by regulation.¹¹⁵ Much of the information that was reported in the ASRs was of limited utility, providing no assurance of the commitment's progress or whether it was en route to completion.¹¹⁶ ASRs are a principal source of drug safety information for the FDA and an important tool for monitoring postmarketing study commitments.¹¹⁷ If a substantial portion of an ASR is missing, and the information that is present is inadequate, ASRs are essentially useless.¹¹⁸ Many reviewers even characterized the monitoring system as "very shallow" because without useful data, drug applicants cannot be encouraged to complete their studies.¹¹⁹ The FDA must take steps to ensure that these commitments are being fulfilled in order for these ASRs to be beneficial.¹²⁰

¹¹³ See HHS OIG, *supra* note 42, at 17 (finding that the FDA often fell short of meeting its own requirements for monitoring postmarketing study commitments); see also Basquill, *supra* note 1, at 84 (asserting that an increase of data that the FDA must review would require greater FDA resources than those already available).

¹¹⁴ See HHS OIG, *supra* note 42, at 12 (noting that even complete ASRs often lacked information that would be useful in monitoring the progress of postmarketing study commitments); see also Neckers, *supra* note 12, at 301 (discussing the poor quality of submitted reports to the FDA).

¹¹⁵ See HHS OIG, *supra* note 42, at 13 (stating that many ASRs were missing important dates); see also Neckers, *supra* note 12, at 302 (stating that the FDA often receives reports with inadequate information or detail).

¹¹⁶ See HHS OIG, *supra* note 42, at 12–13 (stating that inadequate ASRs do not assist in ensuring progress of postmarketing study commitments); see also Basquill, *supra* note 1, at 84–85 (stating that the FDA is "woefully understaffed and under-funded").

¹¹⁷ See HHS OIG, *supra* note 42, at 11 ("ASRs are intended to be a key source of information for FDA and an important tool for monitoring postmarketing study commitments."); see also Curt D. Furberg et al., *The FDA and Drug Safety: A Proposal for Sweeping Changes*, 166 ARCHIVES INTERNAL MED. 1938, 1939 (2006), available at <http://www.ahrp.org/cms/content/view/358/28> (noting that the FDA receives about 400,000 reports a year of serious or unexpected drug safety issues as part of its Adverse Event Reporting System).

¹¹⁸ See HHS OIG, *supra* note 42, at 14 (explaining that ASRs do not give complete information and as a result, reviewers are forced to search for past reports that were submitted by the sponsor); see also Schanz, *supra* note 7, at 496–97 (asserting that about one-third of ASRs are not submitted or are incomplete, and that many of the completed ones lack useful information).

¹¹⁹ See HHS OIG, *supra* note 42, at 13 (noting the claims made by an FDA official that the current process for monitoring commitments is "very shallow" because it does not necessarily move the commitments towards completion); see also Schanz, *supra* note 7, at 495 ("Legally, the maze of regulations governing postmarket obligations by pharmaceutical sponsors leaves considerable opportunity for ambiguity, delays and lack of stringent enforcement measures to motivate compliance.").

¹²⁰ See HHS OIG, *supra* note 42, at 17 (indicating that monitoring postmarketing study comments and ASRs is not a top priority at the FDA); see also Steenburg, *supra* note 2, at 361 (expanding on the notion that because postmarketing demands are no longer a rare exception, completion rates of commitments are expected to decrease).

B. Serious Adverse Events Reporting

1. History

The Office of Surveillance and Epidemiology (OSE) identifies adverse events through two important systems: postmarketing surveillance and risk assessment.¹²¹ Because premarket clinical trials are generally conducted on populations of a few hundred to a few thousand participants,¹²² only a fraction of a drug's practical, long-term effects are discovered.¹²³ As a result, the FDA approves drugs by judging whether the drug's known risks are outweighed by its known benefits.¹²⁴ The purpose of the FDA's postmarketing surveillance system is to collect data on any rare or long term effects of the drug that are not found during pre-approval.¹²⁵ Under 21 C.F.R. § 314.80, all approved NDAs are required to report to the FDA when an adverse drug reaction occurs.¹²⁶ An adverse drug experience

¹²¹ See FDA, Center for Drug Evaluation & Research, Office of Surveillance and Epidemiology, <http://www.fda.gov/Cder/Offices/ODS/default.htm> (last visited Sept. 1, 2008). CDER evaluates drug safety by maintaining a system of postmarketing surveillance and risk assessment programs that identify adverse events that were absent in the drug development process. *Id.* OSE was formerly known as the Office of Drug Safety. *Id.* The CDER website gives a comprehensive view of the CDER's function and how it achieves its goals. See U.S. FDA CDER Home Page, *supra* note 36. While risk assessment is an integral aspect of postmarketing surveillance, it is outside the scope of this note.

¹²² See Syed Rizwanuddin Ahmad, *Adverse Drug Event Monitoring at the Food and Drug Administration: Your Report Can Make a Difference*, 18(1) J. GEN. INTERNAL MED. 57, 57 (2003), available at <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1494803> (noting further that most trials exclude the elderly, pregnant women, patients with multiple diseases, and those on medications suspected of interacting with the study drug); see also Steenburg, *supra* note 2, at 297 ("Preapproval trials involve no more than a few thousand volunteers – often carefully culled and largely homogenous – who are treated under carefully controlled conditions by highly-trained medical specialists.").

¹²³ See Ahmad, *supra* note 122, at 57 (explaining that because the participants in clinical trials are not always representative of the real world where the drug will be used, the safety reporting is not always perfect); see also Basquill, *supra* note 1, at 76 (suggesting that adverse events that are too rare to be noticed during the clinical trials may manifest themselves faster when a population hundreds of times larger is exposed to the drug); Steenburg, *supra* note 2, at 297 (revealing that the FDA commissioner admitted that even the most extensive clinical tests will only reveal a fraction of the information that emerges during the course of a drug's use).

¹²⁴ See GAO, *supra* note 85, at 7 (explaining that if the FDA has reason to believe that a drug on the market poses a threat, it will weigh the effect of that adverse event against the benefit of the drug to determine what actions to take); see also Basquill, *supra* note 1, at 74–75 (indicating that a prescription drug will only be sold after it undergoes a "complex review and approval process" to determine whether it meets agency standards of safety and efficacy).

¹²⁵ CENTER FOR DRUG EVALUATION AND RESEARCH, FDA, ENFORCEMENT OF THE POSTMARKETING ADVERSE DRUG EXPERIENCE REPORTING REGULATIONS (1999), available at <http://www.fda.gov/cder/aers/chapter53.htm> (stating that all sponsors, manufacturers, packers and distributors are required to report serious and unexpected adverse drug experiences to the FDA); see Ahmad, *supra* note 122, at 57 (noting that the FDA monitors the safety of each drug after it reaches the market through the Adverse Event Reporting System, which receives information from the pharmaceutical companies, as well as from physicians, nurses, dentists and consumers).

¹²⁶ 21 C.F.R. § 314.80(c) (2008) ("The applicant shall report to FDA adverse drug experience

(ADE) is any undesirable experience resulting from the use of a drug.¹²⁷ A serious adverse drug experience (SADE) is any adverse event that is life-threatening, or that results in hospitalization, a significant disability or incapacity, a congenital anomaly, or death.¹²⁸ Drug applicants must review any and all ADE information that they obtain or receive from any source.¹²⁹ Upon receipt of any adverse drug experience information, applicants have fifteen days to submit an alert report for each event to the FDA.¹³⁰ A prompt investigation of each adverse drug experience must also be conducted within fifteen calendar days of receipt of new information or as requested by the FDA.¹³¹

OSE is responsible for reviewing these reports of adverse reactions through a spontaneous reporting database called Adverse Event Reporting System (AERS).¹³² AERS is a computerized information database designed to support the FDA's postmarketing safety surveillance program.¹³³ AERS receives information from two primary sources: mandatory reports from sponsors on adverse events that have been spontaneously communicated to them, and adverse event reports from physicians, and other health officials that have voluntarily been submitted to the FDA's MedWatch program.¹³⁴

information, as described in this section.").

¹²⁷ 21 C.F.R. § 314.80(a). The following are a list of events which are included in the definition of adverse drug experience: An adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action. *Id.*

¹²⁸ *Id.* ("Serious adverse drug experience. Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.")

¹²⁹ 21 C.F.R. § 314.80(b). This includes "information derived from commercial marketing experience, postmarketing clinical investigations, postmarketing epidemiological/surveillance studies, reports in the scientific literature, and unpublished scientific papers." *Id.*

¹³⁰ 21 C.F.R. § 314.80(c)(1)(i). "The applicant shall report each adverse drug experience that is both serious and unexpected, whether foreign or domestic, as soon as possible but in no case later than 15 calendar days of initial receipt of the information by the applicant." *Id.*

¹³¹ *Id.* at § 314.80(c)(1)(ii). "The applicant shall promptly investigate all adverse drug experiences that are the subject of these postmarketing 15-day Alert reports and shall submit followup reports within 15 calendar days of receipt of new information or as requested by FDA." *Id.*

¹³² See Ahmad, *supra* note 122, at 57 (discussing the FDA's use of Adverse Event Reporting System). See generally New Molecular Entity (NME) Post-Marketing Safety Evaluation Pilot Program Progress Report, http://www.fda.gov/CDER/drug/postmarketing_safety/progress_report.htm (last visited Oct. 14, 2008) (describing the core function of OSE as reviewing the postmarketing safety of a marketed drug).

¹³³ See FDA, Adverse Event Reporting System (AERS), <http://www.fda.gov/cder/aerssub/default.htm> (explaining how the AERS allows the FDA to efficiently monitor and respond to postmarketing safety reports); see also Shea et al., *supra* note 11, at 446 (describing the Adverse Reporting System).

¹³⁴ See Ahmad, *supra* note 122, at 57 (explaining how the AERS receives information enabling it to perform its oversight function); see also Adverse Event Reporting System (AERS), *supra* note 133

Other reports come from sponsors' clinical studies.¹³⁵ Clinical reviewers evaluate the AERS reports and search for safety "signals," which are previously unrecognized or unlabeled serious adverse events.¹³⁶ Once a signal is found, the next step is to look for additional cases in AERS, medical literature or other databases such as those from foreign regulatory agencies.¹³⁷ After other cases are found, OSE physicians, who frontline the surveillance program, search for any risk factors, common trends, or causal relationships of the drug.¹³⁸ The physicians may then confirm potential signals by conducting studies in one of several large population-based databases that link prescriptions with adverse outcomes.¹³⁹ These studies are primarily conducted by specialized investigators who are affiliated with departments of pharmacoepidemiology and pharmacy, in places such as universities and Health Maintenance Organizations (HMOs).¹⁴⁰

After confirmation of a signal, the FDA must decide whether to take

(describing the AERS in general); FDA, MedWatch, <http://www.fda.gov/medwatch/What.htm> (last visited Oct. 1, 2008)) (noting that MedWatch is the FDA Safety Information and Adverse Event Reporting Program and how it provides information about safety issues involving medical products as well as pharmaceutical drugs); FDA, Voluntary Reporting by Health Professionals, <http://www.fda.gov/medwatch/report/hcp.htm> (last visited Oct. 1, 2008) (explaining how Form FDA 3500 is for voluntary reporting and Form FDA 3500A is for mandatory reporting).

¹³⁵ See GAO, *supra* note 85, at 5–7. Observational studies are also submitted to the FDA for review of adverse events. *Id.* at 6–7. Observational studies are different from clinical studies in that the investigator has no control over the therapy but merely observes. *Id.* at 7 n.11. Whereas in clinical studies, the investigator purposely manipulates the therapy to discover any causal relationships. *Id.* at 7. FDA, GUIDANCE FOR INDUSTRY: GOOD PHARMACOVIGILANCE PRACTICES AND PHARMACOEPIDEMIOLOGIC ASSESSMENT 4 (2005), available at <http://www.fda.gov/CDER/GUIDANCE/6359OCC.pdf>, notes that clinical studies triggering signals of an adverse event may be submitted to the sponsor or directly to the FDA.

¹³⁶ See Ahmad, *supra* note 122, at 58 (noting that postmarketing safety evaluators are the first to scrutinize data submitted to AERS); see also GOOD PHARMACOVIGILANCE PRACTICES, *supra* note 135, at 4 (stating that the quality of the reports is necessary for appropriate and effective evaluation).

¹³⁷ See Ahmad, *supra* note 122, at 58. Some common signs are: temporal association, coherence with existing information or biological plausibility, similar effect in drugs of the same class, dose-response relationship, consistency of the association, and specificity of association. *Id.* Temporal association is when the adverse outcome happens before the target drug was taken, and consistency of the association means the replicability of results. *Id.* GOOD PHARMACOVIGILANCE PRACTICES, *supra* note 135, at 6, states that in addition to AERS, additional cases may be identified through the Vaccine Adverse Events Reporting System (VAERS).

¹³⁸ See GAO, *supra* note 85, at 16 (explaining that the safety evaluators must determine whether the adverse events are drug related); see also Ahmad, *supra* note 123, at 57–58 (emphasizing the importance of physicians' and other health care officials' roles in FDA's postmarketing surveillance system).

¹³⁹ See Ahmad, *supra* note 122, at 58 (noting that the FDA uses extramural investigators to confirm signals); see also GOOD PHARMACOVIGILANCE PRACTICES, *supra* note 135, at 14 (discussing the use of "thorough database search strategies based on updated coding terminology").

¹⁴⁰ See Ahmad, *supra* note 122, at 58 (noting that investigators have access to a variety of databases); see also SUSAN THAUL, CRS REPORT FOR CONGRESS, DRUG SAFETY AND EFFECTIVENESS: ISSUES AND ACTION OPTIONS AFTER FDA APPROVAL 15–16 (2005) (arguing that HMOs or universities might be better situated to perform postmarket reviews than the government).

regulatory action, and if so, what kind of action to take.¹⁴¹ This is done by considering the results of the safety analysis in the context of other factors, such as the availability of other similar drugs and the condition the drug is designed to treat.¹⁴² There are a variety of regulatory actions taken by the FDA if the adverse event is severe enough.¹⁴³ For example, the FDA can require sponsors to send warning letters to prescribers of the drug, identifying the specific hazard, and adding to or strengthening warning information in the drug's labeling.¹⁴⁴ The FDA may also issue public health advisories concerning the specific use of a drug, and may even restrict the distribution of the drug.¹⁴⁵ Furthermore, in rare instances, a drug may be withdrawn from the market either voluntarily by the sponsor, or by the FDA's action.¹⁴⁶ However, drugs have been voluntarily removed in almost all withdrawal cases.¹⁴⁷ While the FDA has limited authority to

¹⁴¹ See Ahmad, *supra* note 122, at 58 (listing factors that may help the FDA decide whether regulatory action is necessary); see also THAUL, *supra* note 140, at 9 (discussing the types of regulatory actions that the FDA might take in response to an adverse event, like letters to health professionals).

¹⁴² See GAO, *supra* note 85, at 17 (explaining that the Office of New Drugs staff within the review divisions determine what, if any, regulatory action should be taken); see also THAUL, *supra* note 140, at 2 (discussing the Congressional hearings regarding COX-2 inhibitors: "[a]fter weighing the evidence on the safety and risk-to-benefit of Vioxx and similar drugs").

¹⁴³ See Ahmad, *supra* note 122, at 58 (noting that factors such as the seriousness of the adverse events, the availability and safety of alternative therapy, and the outcome of past regulatory intervention, are all important considerations in the determining regulatory action); see also THAUL, *supra* note 140, at 9 (suggesting that withdrawal from the market is the most extreme and rarely used action).

¹⁴⁴ Ahmad, *supra* note 122, 58–59. Examples of recent FDA regulatory actions include: the demand of additional postmarketing reports associated with Clozaril, the addition of a black box warning in the labeling of Serzone, and the strengthening of the warnings, precautions, and adverse reactions section of labeling for Actos and Avandia. *Id.* Table 1, "Recent Safety-based Drug Withdrawals" provides a list of recent drug withdrawals and their respective adverse events. *Id.* at 59. Gerald F. Masoudi, *Legal Developments in the Enforcement of Food and Drug Law*, 63 FOOD & DRUG L.J. 585, 587 (2008), comments that the FDA can require sponsors to engage in other communications such as sending letters to health care professionals or disseminating information to health care providers through professional societies.

¹⁴⁵ See Ahmad, *supra* note 122, at 59 (referring to two antifungal treatments, Sporanox and Lamisil, its association for serious hepatic events, and possible association of serious cardiac adverse events); see also Jacobson & Feigal, *supra* note 97, at 539 (showing that among the FDA's communication tools are public health advisories to inform the public).

¹⁴⁶ See 21 U.S.C. § 355(e) (2008) (allowing the FDA to propose withdrawal when it determines that a drug is unsafe under conditions of use approved in its application); see also Ahmad, *supra* note 122, at 59 (noting that the drug cerivastatin "was voluntarily withdrawn from the market by the drug's manufacturer following serious reports of rhabdomyolysis in association with its use"); see also GAO, *supra* note 85, at 10 ("FDA does not have explicit authority to require that drug sponsors take other safety actions; however, when FDA identifies a potential problem, sponsors generally negotiate with FDA to develop a mutually agreeable remedy to avoid other regulatory action.").

¹⁴⁷ See GAO, *supra* note 85, at 10 ("Since 2000 there have been 10 drug withdrawals for safety reasons, and in all of these cases the drug's sponsors voluntarily removed the drug from the market."); see also Richard A. Epstein, *Regulatory Paternalism in the Market for Drugs: Lessons From Vioxx and Celebrex*, 5 YALE J. HEALTH POL'Y, L. & ETHICS 741, 742 (2005) (stating that voluntarily withdrawing a drug from the market leaves open the possibility that the drug can be returned to the market more readily as well as playing a better role before the jury in subsequent litigation).

require that sponsors conduct postmarket safety studies, sponsors will usually agree to revise drug labels or restrict distribution, to prevent removal of the drug.¹⁴⁸

2. Problems with Postmarketing Surveillance System

The collection of ADE is practically the only statutorily-established tool for postmarket surveillance.¹⁴⁹ Although the spontaneous reporting system has been somewhat effective in identifying latent drug-related problems, there is plenty of room for improvement.¹⁵⁰ The majority of problems with the surveillance program can be classified as problems of under-reporting and inadequacy of the information itself.¹⁵¹ Three barriers to reporting of adverse events are: recognizing of ADE, reporting within the institution, and reporting to the FDA.¹⁵² Recognition of a potential relationship between a drug and an adverse event may be difficult due to the common occurrence of certain medical conditions.¹⁵³ If a drug only amplifies the frequency of that medical condition, it will be difficult to distinguish that condition from a true adverse event.¹⁵⁴ Moreover, there is often a time

¹⁴⁸ See GAO, *supra* note 85, at 43 (citing the voluntary withdrawal of Baycol by sponsors after communications concerning the risk of breakdown of muscle fibers); see also Epstein, *supra* note 147, at 741–42, 744 (noting the withdrawal of Vioxx and Rezulin from the market voluntarily after findings concerning the drugs' possibility as a "killer drug").

¹⁴⁹ See Bright, *supra* note 11, at 609 (emphasizing the difference between the number of FDA-created postmarket tools and the number of law-created tools); see also Schanz, *supra* note 7, at 493 (revealing that The Food, Drug, and Cosmetic Act (FDCA) contains a provision permitting the FDA to monitor the progress of drugs postmarket).

¹⁵⁰ See Steenburg, *supra* note 2, at 298 ("Manufacturers are required to pass along reports that they receive from doctors and others in the field, but they have no baseline obligation to develop their own data-gathering efforts or otherwise to track clinical experiences in an organized manner."); see also Barbara J. Evans & David A. Flockhart, *The Unfinished Business of U.S. Drug Safety Regulation*, 61 FOOD & DRUG L.J. 45, 53 (2006) (highlighting the fact that only one to ten percent of all adverse events that occurred were reported to FDA, as well as only one third to one half of all serious adverse events). But see Bright, *supra* note 11, at 609 (stating that the primary basis of ADE surveillance is the least expensive method of monitoring in the world).

¹⁵¹ See Bright, *supra* note 11, at 610 ("Underreporting is such a significant problem that even if steps are taken to increase reporting, independent sources of information on ADE are critical."); see also Ahmad, *supra* note 122, at 58 (discussing the shortcomings of spontaneous reporting, which contribute to underreporting).

¹⁵² Bright, *supra* note 11, at 609 ("There are many barriers to reporting ADE to FDA, which can be divided by reporting step: recognition, reporting within the institution, and reporting to FDA."); see Goldman, *supra* note 16, at 514 (stating that other barriers include the complexities of risk communication and risk management in the postmarketing realm).

¹⁵³ See Bright, *supra* note 11, at 609 (addressing the possible reasons for the lack of recognition of a relationship between a drug and ADE); Steenburg, *supra* note 2, at 299 (arguing that the amplified frequency of medical conditions that commonly occur may be mistaken for a safety "signal").

¹⁵⁴ See GAO, *supra* note 85, at 24 (stating that the magnitude of drug safety problems is difficult to establish because the FDA cannot determine the proper frequency of ADEs using AERS data); see also Bright, *supra* note 11, at 609 (noting that an ADE may go unrecognized if it can be "reasonably explained by other causes").

delay from when a drug is used to the occurrence of the ADE that interferes with establishing causal relationships.¹⁵⁵ The ADE may even occur in a different location of the body from the actual location that was targeted in testing, which further complicates the identification of causal relationships and overall recognition of ADEs.¹⁵⁶

If a potential causal relationship is identified, there are additional obstacles in the reporting phases that reduce the surveillance system's effectiveness.¹⁵⁷ For instance, many ADEs fail to be reported because they are thought to be already known or resolved.¹⁵⁸ Also, those who discover ADEs may be concerned about being blamed for the ADE, and may hesitate to report it.¹⁵⁹ As a result, only a small fraction of the adverse events that occur are actually reported to the FDA.¹⁶⁰ Data reported to the FDA covers only one to ten percent of all adverse events that actually occur, and between one third and one half of all the serious adverse events.¹⁶¹ Thus, the FDA's MedWatch program, although useful, is undermined by the fact that only a small percentage of reports come from healthcare providers and patients.¹⁶²

¹⁵⁵ Bright, *supra* note 11, at 609 (suggesting that a lack of recognition can be explained by the time delay between drug use and ADE); see LEWIS R. GOLDFRANK ET AL., GOLDFRANK'S TOXICOLOGIC EMERGENCIES 1759 (7th ed. 2002) (providing an example of a "type B" ADE that develops over a period of several days to weeks).

¹⁵⁶ Bright, *supra* note 11, at 609. It is possible for an ADE to occur in a different organ system than that being treated by the drug. Cf. Charles L. Bennett & Cara C. Tigue, *Overcoming Barriers to Reporting Adverse Drug Events*, MEDSCAPE PHARMACISTS, May 29, 2008, <http://www.medscape.com/viewarticle/574523>. Often, toxicity profiles of new agents in drugs are not fully characterized at the time of FDA approval. *Id.* Thus, if clinicians are unfamiliar with certain agents and their effect on certain parts of the body, these parts may go untested and the ADE will not be recognized. *Id.*

¹⁵⁷ Bright, *supra* note 11, at 609–10 (stating that even if a relationship between a drug and ADE is recognized, there are still many barriers to reporting ADE); see Ahmad, *supra* note 122, at 58 (discussing the limitations of spontaneous reporting, including poor and infrequent documentation).

¹⁵⁸ See Bright, *supra* note 11, at 610. If an ADE is already known, it is publicized or already listed on the label. *Id.* Martin S. Manno, *Preventing Adverse Drug Events*, 36 NURSING 2006 3 56, 58 (2006) available at http://www.nursingcenter.com/library/JournalArticle.asp?Article_ID=633458, notes that health care professionals may underreport ADEs if the anticipated benefits of a drug outweigh the risk of developing an anticipated adverse reaction.

¹⁵⁹ Bright, *supra* note 11, at 610. "[T]he healthcare provider . . . could be concerned about being blamed for the ADE . . ." *Id.* Another unfortunate reason for under-reporting is as simple as the reporter being too busy. *Id.* Manno, *supra* note 158, at 59, comments that sadly, a person who administers a drug causing ADE is more likely to be blamed than the flawed ADE reporting system.

¹⁶⁰ See Ahmad, *supra* note 122, at 58 (explaining that the extent of under-reporting depends on the severity of the ADE, among several other factors); see also Evans & Flockhart, *supra* note 150, at 53 (criticizing the FDA's failure to use certain periodical reports of adverse events in a "systematic goal-setting process to reduce their frequency").

¹⁶¹ Evans & Flockhart, *supra* note 150, at 53 ("[I]t is estimated that data reported to FDA cover only one to ten percent of all adverse events that actually occur, and between one third and one half of all the serious adverse events."); see Basquill, *supra* note 1, at 79 (indicating that the actual rate of ADE reporting may even be lower than ten percent).

¹⁶² Bright, *supra* note 11, at 610. Manufacturers mostly report to MedWatch and these reports are based on reports from their sales staff or product complaints they received from their customers. *Id.*

Assuming ADEs have been reported, the information itself is frequently poorly documented, forcing the reviewer to contact the reporter.¹⁶³ Contacting the reporter may even require going through the manufacturer first, which significantly delays the overall process.¹⁶⁴ More specifically, problems such as inadequate and incomplete drug descriptions and little or no data on the extent of drug use are all too common.¹⁶⁵ Due to the structure of ADE reports, they often emphasize adverse outcomes and completely neglect successful uses of the drug.¹⁶⁶ Full extent of drug use, including successful use, is imperative for the accuracy of calculations.¹⁶⁷ Similarly, limited information compromises risk calculations, due to the lack of detail in underlying problems of the drug.¹⁶⁸ Altogether, these problems create difficulties in analyzing adverse events and impede the overall surveillance system.¹⁶⁹

Goldman, *supra* note 16, at 522, notes that patients or healthcare providers completed only eighteen percent of reports filed between 1993–1998.

¹⁶³ Ahmad, *supra* note 122, at 58 (“One of the limitations of spontaneous reports is that, in general, they are poorly documented, and the safety evaluator may need to contact the event reporter . . .”); see Cameron Rhudy, *How Congress May Have Failed Consumers with the Food and Drug Administration Amendments Act of 2007*, 27 BIOTECHNOLOGY L. REP. 99, 102 (2008) (citing poor documentation as an “obvious criticism” of MedWatch).

¹⁶⁴ See Ahmad, *supra* note 122, at 58 (suggesting that adequate documentation at the initial stage stands to expedite the entire process); see also Rhudy, *supra* note 163, at 102 (recognizing that corporations are often disinclined to release information that is detrimental to them).

¹⁶⁵ Bright, *supra* note 11, at 610 (calculating the true frequency is difficult, which in turn, makes it difficult to establish the magnitude of a safety problem); see GAO, *supra* note 85, at 24–28 (noting that there are many difficulties in obtaining complete and reliable data experienced by regulatory authorities).

¹⁶⁶ Bright, *supra* note 11, at 610 (“The nature of ADE reports emphasizes cases of adverse outcome and ignores instances of successful use.”); see FDA, MedWatch Reporting Forms, <http://www.fda.gov/medwatch/getforms.htm> (last visited Nov. 8, 2008) (providing only the forms that enable reports of incidents of adverse effects).

¹⁶⁷ Bright, *supra* note 11, at 610 (“Since there is no inherent mechanism for reporting the total amount of both successful and unsuccessful drug use, risks related to drug use are not readily calculated.”); see Struve, *supra* note 94, at 603–04 (suggesting that the amount, quality, and subject matter of reports filed factors into their overall usefulness).

¹⁶⁸ Bright, *supra* note 11, at 610 (“Many significant problems are discovered and addressed by the manufacturers well before FDA recognizes the problem or takes action. Conversely, manufacturers may not sufficiently address problems with their products until FDA also becomes aware of them.”); see Rhudy, *supra* note 163, at 102 (noting the voluntary nature of the reports on which MedWatch relies may result in underreporting).

¹⁶⁹ See Bright, *supra* note 11, at 610 (noting that no one problem is entirely to blame for difficulties in such analysis); see also Steenburg, *supra* note 2, at 298 (commenting on the “difficulty evaluating the data without a clear sense of the relevant ‘denominator’ – the number of people meeting a given profile of interest, often based on demographic and medical factors”).

II. EUROPE AND JAPAN

A. Europe

The European Union's market for pharmaceutical products is highly regulated.¹⁷⁰ Contrary to the U.S., close to eighty percent of pharmaceutical regulatory activity in the EU is devoted to postmarket monitoring and safety.¹⁷¹ Such close attention to postmarketing activity gives rise to two of the largest differences between pharmaceutical regulation in the U.S. and the EU – the EU's system of personal and criminal liability¹⁷² and their extensive inspections program.¹⁷³ The pharmacovigilance program varies under the EU's two decentralized and centralized systems.¹⁷⁴ In the decentralized process, the EMEA is responsible for coordinating pharmacovigilance activities, and ensuring that pharmacovigilance is the "collective responsibility of the member states."¹⁷⁵ The EMEA maintains

¹⁷⁰ See Matthews & Wilson, *supra* note 16, at 407 (discussing examples from the European Union of "widespread monitoring" while on the market "in addition to assessment and pre-market authorization of new pharmaceutical products"); see also Teresa Pechulis Buono, Note, *Biotechnology-Derived Pharmaceuticals: Harmonizing Regional Regulations*, 18 SUFFOLK TRANSNAT'L L. REV. 133, 158 (1995) (examining the EU's recognition of environmental considerations in the approval process).

¹⁷¹ See Matthews & Wilson, *supra* note 16, at 419 (positing that pharmacovigilance, the EU's system for postmarketing regulation, is "a time-consuming process comprising 80 percent of pharmaceutical regulatory activity"); see also Goldman, *supra* note 16, at 527 (discussing the EU regulatory documents which provide detailed guidance for postmarket surveillance).

¹⁷² See Goldman, *supra* note 16, at 524 (noting that the pharmacovigilance system in Europe "is under strict legal obligations entailing personal financial and criminal liability"); see also Matthews & Wilson, *supra* note 16, at 416 (indicating that liability is borne by institutions themselves and not simply the countries that recommended market authorization for the product).

¹⁷³ See European Comm'n, *Volume 9A of the Rules Governing Medicinal Products in the European Union: Guidelines on Pharmacovigilance for Medicinal Products for Human Use*, 29–33 (Mar. 2007) [hereinafter *Volume 9A*], available at http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-9/pdf/vol9_2007-07_upd07.pdf (detailing the various types of pharmacovigilance inspections); see also Goldman, *supra* note 16, at 527–28 (describing the pharmacovigilance inspection process).

¹⁷⁴ See Matthews & Wilson, *supra* note 16 at 408–20. Pharmaceutical regulation in the EU has developed into a centralized and decentralized market. *Id.* at 420. First, the 1965 Directive 65/65/EEC created a centralized framework for pharmaceutical approval. *Id.* at 408. The Committee for Proprietary Medicinal Products (now known as the CHMP), was also developed to function as a "central clearinghouse for drug approvals submitted to any single European State." Thomas, *supra* note 59, at 374 (quoting David V. Eakin, *The International Conference on Harmonization of Pharmaceutical Regulations: Progress or Stagnation?*, 6 TULSA J. COMP. & INT'L L. 221, 224 (1999)). Under the multi-state procedure for authorization, if a manufacturer was approved by at least one state, it could apply for approval in up to five other states in the EU. *Id.* at 374–75. However, discretion of approval was left to each state's regulatory agencies. *Id.* at 374. In 1993, problems with the multi-state procedure led to the development of the European Medicines Evaluation Agency (EMA), which "provide[d] a centralized system for approving pharmaceuticals." *Id.* at 374. Although EMA approves pharmaceutical sales in any EU nation, the option of single-state approval still exists, and is now referred to as decentralized mutual recognition. Matthews & Wilson, *supra* note 16, at 412. A third method of approval is "a country-by-country basis via national registration procedures," which primarily applies to new drug applicants. *Id.*

¹⁷⁵ Matthews & Wilson, *supra* note 16, at 420.

clinical results, as well as a database of reports of serious reactions to drugs that were approved through mutual recognition.¹⁷⁶ Pharmacovigilance in the centralized procedure is executed by the CHMP, which monitors any variations or modifications to an existing market authorization.¹⁷⁷ The CHMP analyzes evidence and formulates opinions on emerging safety concerns.¹⁷⁸ Postmarket monitoring is conducted through the EU's network of national medicines agencies, in close cooperation with healthcare professionals and the pharmaceutical companies themselves.¹⁷⁹ Volume 9A of the Rules Governing Medicinal Products in the European Union: Guidelines on Pharmacovigilance for Medicinal Products for Human Use, is a complete set of guidelines, requirements, procedures and roles for both Marketing Authorization Holders (drug manufacturers/sponsors) and Competent Authorities (regulatory bodies of each EU state).¹⁸⁰ The majority of pharmacovigilance legislation is contained in Chapter 3 of Regulation (EC) No 726/2004 and Title IX of Directive 2001/83/EC.¹⁸¹

Under this authority, each MAH must ensure that it has an appropriate system of pharmacovigilance and risk management in place in order to

¹⁷⁶ Thomas, *supra* note 59, at 375 ("The EMEA maintains clinical outcomes evidence of pharmaceuticals approved through the centralized system. It also compiles and maintains reports from national regulatory bodies of 'serious' reactions to pharmaceuticals approved through mutual recognition."); see Markus Schott, *Medical Research on Humans: Regulation in Switzerland, the European Union, and the United States*, 60 FOOD & DRUG L.J. 45, 63 (2005) (stating that every EU country must enter a European-wide database, which is only open to the countries' "competent authorities, the Commission, and the [EMEA], which operates it").

¹⁷⁷ Matthews & Wilson, *supra* note 16, at 420 ("Under the centraliz[ed] procedure, pharmacovigilance work is carried out by the CPMP . . ."); see EMEA, Overview of the Committee for Medicinal Products for Human Use (CHMP), <http://www.emea.europa.eu/htmls/general/contacts/CHMP/CHMP.html> (enumerating the various responsibilities of the CHMP, which include "several post-authoriz[ation] and maintenance activities").

¹⁷⁸ See Volume 9A, *supra* note 173, at 16. "The Agency's scientific committee, the CHMP . . . is responsible for evaluating evidence and formulating Opinions on emerging safety concerns with centrally authoriz[ed] products . . ." *Id.* If a drug is deemed hazardous, EMEA's "rapid alert" system notifies other national authorities, and a formal CHMP Opinion is published. Matthews & Wilson, *supra* note 16, at 420. The Opinion is a determination on whether the drug should be withdrawn from the market. *Id.* Because the publication may take up to six months, the product may be suspended from the market until a final determination is issued. *Id.*

¹⁷⁹ See EMEA, *supra* note 177 (noting that for every centrally authorized product on the market, a European Public Assessment Report (EPAR) is published, providing scientific data as to the reasons for granting authorization, as well as a summary of product characteristics); see also Richard F. Kingham et al., *The New European Medicines Agency*, 49 FOOD & DRUG L.J. 301, 313-14 (1994) (describing the reporting process, which involves the agencies, healthcare professionals, and the pharmaceutical companies).

¹⁸⁰ See Volume 9A, *supra* note 173, at 13 (describing the purpose of the guidelines in EC Volume 9A); see also Goldman, *supra* note 16, at 527 (noting the guidance that Volume 9A provides).

¹⁸¹ See Volume 9A, *supra* note 173, at 14 (providing the legal framework for pharmacovigilance); see also Thomas Gehring & Sebastian Krapohl, *Supranational Regulatory Agencies Between Independence and Control: The EMEA and the Authorization of Pharmaceuticals in the European Single Market*, 14:2 J. EUR. PUB. POL'Y 208, 218 (2007) (describing Regulation (EC) 726/2004 and Directive 2001/83/EC as the sources for legal criteria concerning testing of human medicine).

assure responsibility and liability for its products on the market and to ensure that appropriate action can be taken.¹⁸² Article 8(3)(n) of Directive 2001/83/EC mandates that MAHs appoint a Qualified Person Responsible for Pharmacovigilance (QPPV).¹⁸³ This is one of the most effective features of pharmacovigilance, and ensures compliance from manufacturers and promotes drug safety. A QPPV is responsible for maintaining the database of information about all suspected adverse reactions that are easily accessible to the EU.¹⁸⁴ A QPPV must prepare Adverse Reaction reports and Periodic Safety Update Reports (PSUR), monitor the safety of a product throughout its lifetime, and respond to requests for information from other agencies.¹⁸⁵ A QPPV is financially and criminally liable for failure to fulfill these postmarketing obligations.¹⁸⁶ Highly detailed descriptions of the pharmacovigilance system, organizational charts, documented procedures, and comprehensive databases are among the many requirements a QPPV must fulfill, and are set out in Volume 9A.¹⁸⁷

The pharmacovigilance program also has a specialized Inspections provision. Inspections of a MAH's pharmacovigilance systems are either routine or 'for cause' and are conducted by the Competent Authority of the state in whose territory the QPPV is located.¹⁸⁸ National inspection

¹⁸² See *Volume 9A, supra* note 173, at 15 (describing the responsibilities of MAH); see also Ivana Hanzl-Dujmović et al., *Issues with Regulatory Pharmacovigilance in East European Countries: The Industry Perspective*, 2007 TOXICOLOGY LETTERS 168, 228–29 (outlining the new requirements for pharmacovigilance in the European Union).

¹⁸³ *Volume 9A, supra* note 173, at 18. "QPPV should be appropriately qualified, with documented experience in all aspects of pharmacovigilance in order to fulfill the responsibilities and tasks of the post. If the QPPV is not medically qualified, access to a medically qualified person should be available." *Id.* A QPPV should "[h]ave experience in all aspects of pharmacovigilance and if not medically qualified (do not have a medical degree) should report to, or have access to a medically qualified person." MHRA, Qualified Persons for Pharmacovigilance, http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=680 (last visited Oct. 1, 2008).

¹⁸⁴ See *Volume 9A, supra* note 173, at 19 (describing the role of the QPPV as overseer of the pharmacovigilance QPPV); see also MHRA, *supra* note 183 (listing that a QPPV is responsible for "[t]he establishment and maintenance of a system which ensures that information about all suspected adverse reactions which are reported to the personnel of the registration holder . . . is collected and collated in order to be accessible at least at one point within the Community").

¹⁸⁵ See Council Regulation 726/2004, art. 24, 2004 O.J. (L 36) 1 (EC) (ordering the creation of safety reports and describing their distribution); see also MHRA, *supra* note 183 (listing the responsibilities of the QPPV).

¹⁸⁶ See Goldman, *supra* note 16, at 524. QPPV serves as an advocate for compliance of pharmacovigilance activities. U.S. currently has no one like QPPV in its system. *Id.* The criminal and financial liability extends to the institution that authorizes the product. See Matthews & Wilson, *supra* note 16, at 416.

¹⁸⁷ *Volume 9A, supra* note 173, at 21–25 (describing the requirements of MAH in applying for its authorization and how it is to maintain its pharmacovigilance program).

¹⁸⁸ See *Id.* at 29 (providing guidance on pharmacovigilance inspections); see also Patricia Fitzgerald, *Pharmacovigilance Inspections*, 40 INDIAN J. OF PHARMACOLOGY S21, S21 (2008) (detailing inspection procedures in the UK).

programs, such as the UK's Medicine and Healthcare products Regulatory Agency (MHRA), generally conduct these inspections.¹⁸⁹ Routine inspections are used to determine whether a MAH has the necessary personnel, systems, and facilities in place to meet its regulatory obligations.¹⁹⁰ 'For cause' inspections are those that are triggered by safety issues, suspected violations of pharmacovigilance legislation, or by request of the CHMP.¹⁹¹ MHRA requires MAHs to complete a Summary of Pharmacovigilance Systems (SPS), which assists the MAH and the Inspectorate to prepare for the inspection.¹⁹² The Pharmacovigilance Inspectorate Unit of MHRA consists of inspectors who have acquired a certain level of expertise in their specialized fields.¹⁹³ As a result, they are able to gain a deep understanding in their specialized areas.¹⁹⁴ The inspections themselves consist of site visits during which interviews, document and computer system reviews (including searches of any pharmacovigilance databases) are performed.¹⁹⁵ If a MAH fails to comply

¹⁸⁹ See *Volume 9A*, *supra* note 173, at 30 (explaining that the Competent Authority of the Member State is responsible for the inspection of the pharmacovigilance system in the territory where the QPPV is located); see also MHRA, About Us, http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&noId=20 (last visited Oct. 1, 2008) (describing MHRA's goals and functions in the UK); MHRA, Inspections and Standards: Good Pharmacovigilance Practice, http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&noId=826 (last visited Oct. 1, 2008) [hereinafter *Inspections and Standards*] (stating that UK MAHs undergo routine national inspections on a periodic basis).

¹⁹⁰ See *Volume 9A*, *supra* note 173, at 30 (discussing how inspections determine that the Market Authorization Holder's personnel, systems, and facilities are pursuant to the regulatory obligations for centrally authorized products); see also *Inspections and Standards*, *supra* note 189 (commenting that the inspections are meant to ensure that the systems and procedures used by MAHs comply with existing EU and national pharmacovigilance regulations and guidance).

¹⁹¹ *Inspections and Standards*, *supra* note 189; see *Volume 9A*, *supra* note 173, at 30–31. Triggers for inspection that relate to specific concerns about a product's safety or actual non-compliance include: delays in carrying out or failure to carry out specific obligations or follow-up measures, delays in reporting, incomplete reporting, submission of poor quality or incomplete PSURs, etc. *Volume 9A*, *supra* note 173, at 31. Triggers that do not relate to concerns about a product's safety are: MAH has not previously been inspected, MAH has placed their first product on the market in the EEA, MAH has recently been or is involved in merger or takeover process, and MAH has changed their system significantly. *Id.*

¹⁹² See *Inspections and Standards*, *supra* note 189 (explaining that MAHs are required to complete and submit a Summary of Pharmacovigilance Systems (SPS) document to the lead inspector which assists in preparing for inspection); see also *MHRA Statutory Pharmacovigilance Inspection*, MHRA, June 2006, available at http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&noId=21423&noSaveAs=1&Rendition=WEB (describing SPS as an invaluable tool used to aid the Pharmacovigilance Inspectorate in planning and preparation for upcoming inspections).

¹⁹³ See Goldman, *supra* note 16, at 528. The inspectors generally specialize in physics, pharmacy, chemistry, informational technology and biology. *Id.* Each inspector holds a warrant to assess compliance with medical legislation. See *Inspections and Standards*, *supra* note 189.

¹⁹⁴ See *Volume 9A*, *supra* note 173, at 31 (noting that product-specific inspections require the inspector to focus specifically on a given product); Goldman, *supra* note 16, at 527–28 (contrasting MHRA's Inspectorate with FDA's inspectors).

¹⁹⁵ See *Volume 9A*, *supra* note 173, at 29 (indicating that the results of an inspection are provided to Marketing Authorization Holder who will use the results to improve compliance and possibly as the

with pharmacovigilance legislation, the EMEA, the European Commission, or the competent Authority of the state will take necessary regulatory action.¹⁹⁶

The chief obligation of Competent Authorities is to establish pharmacovigilance systems that are compatible with the procedures undertaken in other Member States and the Agency, in order that pertinent data may be shared between Member States and EMEA.¹⁹⁷ Each state should have a spontaneous reporting program that allows for the collection, maintenance and organization of suspected adverse reaction reports, as well as other types of reports.¹⁹⁸ In the centralized process, the Member States, the European Commission, and the EMEA, all have unique roles and responsibilities that contribute to the overall pharmacovigilance process.¹⁹⁹ Member States must be able to provide adverse reaction information to the EMEA, and identify safety concerns through a national pharmacovigilance system.²⁰⁰ The EMEA's role is to continuously collect and coordinate information on pharmacovigilance systems for all centrally authorized products.²⁰¹ The European Commission serves as the enforcement of legal

basis for enforcement action); Inspections and Standards, *supra* note 189 (explaining that inspectors have a right under Medicines Act 1968 to enter premises covered by the act to conduct inspections, take samples, require the production of books, and to take copies of the books and documents).

¹⁹⁶ See *Volume 9A, supra* note 173, at 33. Regulatory action ranges from additional inspections, to warnings, and possibly even revocation of authorization of the drug. *Id.* "In the event that the overall risk-benefit balance is considered to be unfavourable and proposed risk minimi[z]ation measures are considered inadequate to redress the balance, the medicinal product should be withdrawn from the market and Healthcare Professionals and Patients/the public should be informed as appropriate." *Id.* at 106.

¹⁹⁷ See *Id.* at 109 (proscribing the pharmacovigilance systems that must be established); see also Inspections and Standards, *supra* note 189 (describing the function of the Unit as to assess pharmaceutical companies compliance with EU and UK legislation in terms of monitoring the safety of medicines given to patients).

¹⁹⁸ See *Volume 9A, supra* note 173, at 110. "Each Member State should have in place a system for the collection of spontaneous suspected adverse reaction reports from Healthcare Professionals, Marketing Authori[z]ation Holders and, where appropriate, from Patients/Consumers." *Id.* Other duties include: receipt, validation, and processing of individual case safety reports, signal detection, assessing periodic safety update reports, and evaluating data from company-sponsored post-authorization safety studies, etc. *Id.* at 111–16. Competent authorities of Member States are required to collect and report all relevant information concerning suspected adverse reactions to the Authority. See Commission Regulation 726/2004, art. 22, 2004 O.J. (L136) 12.

¹⁹⁹ See *Volume 9A, supra* note 173 at 123 (stating that pharmacovigilance is based on the respective roles and obligations of each party). See generally Commission Regulation 726/2004, *supra* note 198, at 1 (providing explicit Community procedures for the authorization and postmarketing supervision of medicinal products, and establishing the EMEA as the centralized authority for approving pharmaceuticals).

²⁰⁰ See *Volume 9A, supra* note 173, at 131 (listing the specific roles and responsibilities of Member States); see also Commission Regulation 726/2004, *supra* note 198, at art. 28 (mandating all Member States to continually develop pharmacovigilance systems to ensure public safety).

²⁰¹ See *Volume 9A, supra* note 173 at 124 (noting the role of the Agency as the coordinator of the pharmacovigilance system); Commission Regulation 726/2004, *supra* note 198, at art. 25 (stating the Agency's obligation of collecting and forwarding information provided by Member States to the

requirements and decisions by Member States and MAHs.²⁰² Under mutual recognition, the Reference Member State (the first state that approved the drug), usually leads in the analysis and monitoring of such serious adverse reactions.²⁰³ Clearly, Volume 9A provides much greater detail as to which pharmacovigilance activities should be covered by written procedures and better reflects both the latest methods and risk management paradigm that prevails internationally.²⁰⁴

B. Japan

In Japan, postmarketing surveillance of pharmaceuticals and medical devices is of greater importance than premarket and manufacturing functions.²⁰⁵ Unlike the U.S., Japan devotes much of its time and effort into regulating postmarket activities. Japan focuses on precautionary phases and early intervention, as well as the reexamination/reevaluation periods to ensure the drug's continuing safety and efficacy.²⁰⁶ In recent years, the Ministry of Health, Labor and Welfare (MHLW) has increased its

national pharmacovigilance systems).

²⁰² See Volume 9A, *supra* note 173, at 132. The European Commission is responsible for "[e]nforcement of legal requirements and enforcement of the implementation of Decisions by Member States and Marketing Authori[z]ation Holders." *Id.* The Rapporteur is responsible for evaluating and reaching conclusions on issues of post-authorization for centrally authorized drugs. *Id.* The regulation sets forth procedures to be taken by the Commission when a manufacturer or importer is suspected of failing to meet obligations set forth by the governing Directive, 2001/83/EC, on the Community code relating to medicinal products for human use. See Commission Regulation 726/2004, *supra* note 198, art. 20.

²⁰³ See Volume 9A, *supra* note 173, at 138. RMS has the responsibility for evaluating all safety concerns relevant to MRP or DCP products for providing Assessment Reports to the CMS. *Id.* The CHMP Pharmacovigilance Working Party (PhVWP) serves as the discussion forum for all safety concerns relating to the mutual recognition process. *Id.* Authorization Holders are required to obtain information regarding all suspected serious adverse reactions from the reference Member State. See Council Directive 2001/83/EC, art. 104(5)–104(6), 2001 O.J. (L311) 96.

²⁰⁴ See Goldman, *supra* note 16, at 527 (arguing that the Volume 9A guidelines "provide much greater detail as to which pharmacovigilance activities should be covered by written procedures, and better reflect both the latest methods and risk management paradigm that prevails internationally"); see also Schanz, *supra* note 7, at 495–97 (noting that in 2007, the Institute of Medicine released a report titled "The Future of Drug Safety," which found the FDA's postmarketing study commitments to be lacking in priority).

²⁰⁵ See Neckers, *supra* note 12, at 306. Japan's Ministry of Health, Labor and Welfare placed greater importance on postmarketing surveillance of pharmaceutical and medical devices than in premarket functions. *Id.* In 2002, Japan enacted revisions of the Pharmaceutical Affairs Law by placing greater emphasis on postmarketing duties, which reflected the government's efforts to ensure safety and efficacy of medical products. See Martin A. Yahiro & Kiyohito Nakai, *Japan's New Regulatory System*, MEDICAL DEVELINK, Oct. 2004, available at <http://www.device-link.com/mddi/archive/04/10/015.html>.

²⁰⁶ See Neckers, *supra* note 12, at 306 (stating that early postmarketing phase vigilance is one of Japan's several initiatives to enhance prominence in the medical industry); see also Yahiro & Nakai, *supra* note 205 (noting that Japan's revisions to PAL was an effort to ensure the safety and efficacy of medical products).

postmarketing efforts through various initiatives.²⁰⁷ One of the main goals of the revised Pharmaceutical Affairs Law of 2002 (PAL) was to reinforce postmarketing safety regulations, by including reexamination of new drugs, and the reevaluation of drugs.²⁰⁸ With the revised PAL, came the establishment of the revised Good Post-marketing Surveillance Practice (GPMSP) law, which was then divided into two parts.²⁰⁹ The first component, the Good Post-marketing Study Practice (GPSP) involves the collection and preparation of materials for reexamination and reevaluation.²¹⁰ The GPSP specifies items that are to be strictly complied with in order to achieve appropriate post-marketing surveillance and studies conducted by manufacturers/distributors, and to assure the reliability of data submitted when applying for reexamination or reevaluation.²¹¹ The GPSP consists of twelve articles.²¹² Manufacturers or

²⁰⁷ See Neckers, *supra* note 12, at 306. Taking international conformity into account, the revised PAL incorporated ICH's postmarketing surveillance theme. *Id.* The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is an attempt to harmonize the pharmaceutical rules and regulations of the U.S., Europe, and Japan, and ultimately increases the effectiveness, quality and safety of medicines. See International Conference on Harmonisation, <http://www.ich.org/cache/compo/276-254-1.html> (last visited Oct. 1, 2008). MHLW regulates pharmaceutical affairs through its multiple bureaus. Neckers, *supra* note 12, at 306. Established in April 2004, the Pharmaceutical and Medical Devices Agency (PMDA) is an independent administrative organization that is responsible for reviewing postmarketing and safety measures. See Japan Pharmaceuticals Manufacturers Ass'n, English Regulatory Information Task Force, *Pharmaceutical Administration and Regulations in Japan*, at 13 (2006), available at <http://www.jpma.or.jp/english/pajr/pdf/2006.pdf> [hereinafter JPMA, ERITF]. Within the PMDA are thirteen different departments, and one office, each with varying duties. *Id.*

²⁰⁸ See Neckers, *supra* note 12, at 298 (stating that the PAL was revised based on demands for augmentation of safety assurance in keeping with the age of modern science and policies); JPMA, ERITF, *supra* note 207, at 13 (explaining that the revisions were meant to address the enhancements in the development and safety of new medical products in the twenty-first century).

²⁰⁹ See JPMA, ERITF, *supra* note 207, at 103–04. The original GPMSP was merely an administrative notification, rather than official law. *Id.* at 103. Under the 2004 PAL, the GPMSP was “separate[ed] between the part that deals with the collection, preparation and consideration of information for appropriate use of post-marketing safety measures . . . and the part that deals with tests and surveillance conducted to collect and prepare materials for reexamination and reevaluation.” *Id.* at 104. Katharine Neckers' article traces the development of PAL law. See generally Neckers, *supra* note 12, at 297–98.

²¹⁰ JPMA, ERITF, *supra* note 207, at 104 (stating that in the revised PAL enforced in 2004, there is a separation between the part that deals with the collection, preparation and consideration of information for appropriate use of post-market safety measures of the MHLW Ordinance on GPMSP related to the implementation of safety assurance measures, and the part that deals with tests and surveillance conduct to collect and prepare materials for reexamination and reevaluation); see Neckers, *supra* note 12, at 313–14 (noting that the first revision of the medical device regulations brought the enforcement of the regulations to the level of international norms of the Standards for Collection and Preparation of Material Concerning Approval Examination, as well as to the level required by Good Laboratory Practices).

²¹¹ See JPMA, ERITF, *supra* note 207, at 104 (“These standards set forth the items that must be strictly complied with by manufacturers/distributors of drugs in conducting post-marketing surveillance and studies.”); see also Neckers, *supra* note 12, at 324 (claiming that postmarketing surveillance is perhaps the most crucial phase in the development and manufacturing process of new drugs and devices and without such strict regulations, recalls will continue in the future).

distributors of drugs conduct post-marketing surveys for the purpose of collecting, screening, confirming or verifying information that relates to the quality, efficacy, and safety of drugs.²¹³ Compliance surveys are an integral part of the reexamination and reevaluation processes of the GPSP.²¹⁴ These surveys are performed by employees of the Pharmaceutical and Medical Devices Agency (PMDA) and are used as the basis of a data compliance survey – after which a determination of the manufacturer's compliance or non-compliance is made.²¹⁵

The second component, the “Good Vigilance Practice” (GVP), “establishes standards for post-marketing safety management related to the collection, preparation, and study of proper use of information on drugs, etc., and to the implementation of measures for safety assurance.”²¹⁶ The GVP is outlined in sixteen articles.²¹⁷ A recent initiative called early phase postmarketing vigilance (EPPV) aims “to have pharmaceutical companies provide and draw attention of medical professionals to accurate information

²¹² JPMA, ERTIF, *supra* note 207, at 104–08. Article 1 states the purpose of the GPSP standards. *Id.* at 104. Article 2 defines terms such as post-marketing surveys, drug use-result survey, special drug use-results survey, and post-marketing clinical study. *Id.* at 105. Article 3 specifies standard operating procedures for post-marketing surveillance. *Id.* at 105. Article 4 declares the obligations of supervisors of post-marketing surveys. *Id.* at 106. Article 5 specifies the use of post-marketing surveys. *Id.* at 106. Article 6 specifies the use of drug use-results surveys. *Id.* at 107. Article 7 specifies the use of post-marketing clinical studies. *Id.* at 107. Article 8 provides rules concerning in-house inspections. *Id.* at 107. Article 9 details the education and training that a supervisor of post-marketing surveys must have. *Id.* at 107. Article 10 delegates duties of post-marketing surveys. *Id.* at 108. Article 11 describes the process of preserving records in connection with post-marketing surveys. *Id.* at 108. Article 12 sets the standards for compliance of reexamination and reevaluation of data in connection with post-marketing surveillance. *Id.* at 108.

²¹³ *Id.* at 105 (clarifying that drug use-results surveys, special drug use-results surveys, and post-marketing clinical studies are other examples of surveys that are conducted by drug manufacturers); see Neckers, *supra* note 12, at 306 (reporting that cooperation from regulatory authorities and healthcare providers in funding these postmarket surveillance systems is also necessary for vast improvement).

²¹⁴ See JPMA, ERTIF, *supra* note 207, at 108 (noting that the surveys are implemented in accordance with the Guidance for Implementation of GPSP On-site surveys established by the MHLW); see also THE WORKING GROUP, THE JAPAN SOCIETY FOR PRECISION ENGINEERING, FUTURE POSTMARKETING SURVEILLANCE (PMS) IN JAPAN 4 (Yuka Ohgaki, Fumiko Miyaji, & Mikihiro Kosuge trans., 2003) [hereinafter JAPAN SOCIETY FOR PRECISION ENGINEERING], available at http://www.jspe.jp/pms_pdf/pms_en.pdf (specifying the ADR/infection reporting, reexamination and reevaluation as the major regulatory requirements for marketed drugs in Japan).

²¹⁵ See JPMA, ERTIF, *supra* note 207, at 1 (explaining the role of PMDA); see also Neckers, *supra* note 12, at 315 (describing PMDA as the cornerstone of Japan's medical product regulation).

²¹⁶ JPMA, ERTIF, *supra* note 207, at 109.

²¹⁷ *Id.* at 109–17. Article 1 establishes the purpose of GVP. *Id.* at 109. Article 2 lists definitions of terms: safety management information, quality assurance activities, early post-marketing surveillance, and persons in charge of drug information and medical device information. *Id.* Articles 3 to 12 specify the duties and obligations of general manufacturing/distribution supervisors. *Id.* at 109–16. Article 13 provides standards for post-marketing safety management of type 2 manufacturers/distributors. *Id.* at 116. Article 14 provides standards for post-marketing safety management of type 3 manufacturers/distributors. *Id.* Article 15 describes retention of records related to safety assurance. *Id.* Article 13 and 14 both deal with standards for post-marketing safety management of type 2 manufacturers/distributors. *Id.*

and promote understanding of proper use over a period of 6 months from the launch of new products”²¹⁸ This rapid collection of information on serious adverse reactions would allow the MHLW to minimize the harmful effects that people may experience.²¹⁹ This postmarketing vigilance phase is invaluable because it produces “thorough dissemination of information on proper use and early acquisition of ADR information.”²²⁰

Like the U.S. and EU, Japan also has an adverse drug reaction reporting system, however, as previously mentioned, Japan implemented additional systems for reexamination and reevaluation.²²¹ The three main bodies of the reporting system are: the MHLW’s drug safety information reporting system, the adverse drug reaction reporting system by pharmaceutical companies, and the World Health Organization’s (WHO’s) International Drug Monitoring Program.²²² The MHLW’s system collects safety information from health professionals and all medical institutions and pharmacies directly.²²³ Any adverse event, including well-known adverse events, associated with the drug must be reported.²²⁴

Pharmaceutical companies, in accordance with the PAL, are obligated to report adverse drug reactions and infections, serious cases, as well as regulatory information, such as measures adopted in foreign countries to

²¹⁸ Neckers, *supra* note 12, at 308 (quoting Japanese Pharmaceutical Manufacturers Association, One Year After Early Post-marketing Phase Vigilance Surveillance, http://www.jpma.or.jp/english/events/topics/update/update25_g.html (last visited Oct. 1, 2008) [hereinafter JPMA, One Year After]).

²¹⁹ See JPMA, One Year After, *supra* note 218 (stating that EPPV requests “companies to cooperate in collection of ADR information and to take the necessary safety measures”); see also Akira Kawahara, *Post-Marketing Safety Measures in Japan*, Apr. 2008, at 36, available at <http://www2.convention.co.jp/eaprs2008ph/presen/0414-B2-03.pdf> (noting that the MHLW/PMDA’s mission statement is “to ensure faster access to more effective and safer pharmaceuticals, medical devices for the public”).

²²⁰ Neckers, *supra* note 12, at 309 (quoting JAPAN SOCIETY FOR PRECISION ENGINEERING, *supra* note 214, at 15).

²²¹ See JPMA, ERITF, *supra* note 207, at 24 (providing the necessary procedures that manufacturers/distributors must perform as part of the reexamination and reevaluation process); see also Neckers, *supra* note 12, at 307 (stating that unlike Japan, “the United States does not employ re-examination and re-evaluation requirements”).

²²² See JPMA, ERITF, *supra* note 207, at 117 (describing each of the three main bodies); see also MHLW, White Paper: Annual Report on Health and Welfare, Approval and Licensing System for Drugs, Quasi-Drugs and Cosmetics, http://www1.mhlw.go.jp/english/wp_5/vol2/p2c5.html (last visited Oct. 1, 2008) [hereinafter White Paper Report] (providing a chart of the structure of postmarketing safety measures).

²²³ See JPMA, ERITF, *supra* note 207, at 117 (stating that “the reporting format has been simplified in order to further increase the number of reports from physicians, dentists, and pharmacists”); see also Kawahara, *supra* note 219, at 12–13 (outlining two models of information flow).

²²⁴ JPMA, ERITF, *supra* note 207, at 117–19. Only “mild, well-known adverse events” do not have to be reported. *Id.* at 117. Certain adverse events must be reported within 15 days when they are first known, while others must be reported within 30 days. *Id.* at 118–19.

discontinue manufacturing and/or distribution of a drug due to safety concerns.²²⁵ Certain adverse drug reactions are required to be reported within fifteen days of the time that they are first discovered.²²⁶ These cases include: death, disability, and any other serious problems that may lead to death.²²⁷ Other types of adverse reactions are to be reported within thirty days from the time that they are first known.²²⁸ The WHO's international drug monitoring program collects data from member states, creates a summary of the results, and sends the summary report to each country.²²⁹ The information that the MHLW receives from the other two bodies of the system is then evaluated and any results must be approved by the PAFSC.²³⁰ Any administrative and regulatory action is also determined at this stage.²³¹

Japan's reexamination system is "aimed at reconfirmation of the clinical usefulness of drugs by performing GPSP or GVP as one aspect of PMS [Postmarketing Strategy], through collecting information on the efficacy

²²⁵ See JPMA, ERITF, *supra* note 207, at 118 (explaining Japan's standard operating procedures for post-marketing safety management); see also Katherine A. Davis, *An International Drug Administration: Curing Uncertainty in International Pharmaceutical Product Liability*, 18 NW. J. INT'L L. & BUS. 685, 720 (1998) (discussing Japan's pharmaceutical regulation procedures).

²²⁶ See JPMA, ERITF, *supra* note 207, at 118. This fifteen-day requirement was "intended to assure focused supervision of serious cases caused by adverse reactions of drugs with little post-marketing clinical experience and to coordinate reporting criteria for adverse drug reactions with international standards." *Id.* Article 62-2 of the Enforcement Regulations requires adverse reactions to be reported by the manufacturer or in-country caretaker to the MHW. See G.R. HIGSON, MEDICAL DEVICE SAFETY: THE REGULATION OF MEDICAL DEVICES FOR PUBLIC HEALTH AND SAFETY 88 (2002).

²²⁷ JPMA, ERITF, *supra* note 207, at 118-19 (stating examples of adverse drug reactions that must be reported to the MHLW within fifteen days); see HIGSON, *supra* note 226, at 88 (noting that in addition to death and disability, adverse reactions that are caused by suspected deficiencies in medical devices used in Japan must also be reported within fifteen days).

²²⁸ JPMA, ERITF, *supra* note 207, at 119 (listing the cases that "must be reported within 30 days from the time they are first known"); see HIGSON, *supra* note 226, at 88 (distinguishing the adverse drug reactions that must be reported within thirty days, as opposed to fifteen).

²²⁹ JPMA, ERITF, *supra* note 207, at 120. The World Health Organization's drug monitoring program facilitates the dissemination of information of adverse drug reactions to participating member states. *Id.* Japan recently became a member of this program in 1972. *Id.* The monitoring program is a collaborative effort between member states, including Japan, to manage drug safety. See The World Health Organization - Uppsala Monitoring Center, WHO Programme for International Drug Monitoring, <http://www.who-umc.org/DynPage.aspx?id=13140> (last visited Sept. 1, 2008).

²³⁰ JPMA, ERITF, *supra* note 207, at 8, 120. The MHLW evaluates drug safety information received in consultation with PAFSC regarding adverse drug reactions. *Id.* at 120. The Pharmaceutical Affairs and Food Sanitation Council (PAFSC) advises the MHLW, and reviews and discusses important pharmaceutical and food sanitation-related matters. *Id.* at 8.

²³¹ See JPMA, ERITF, *supra* note 207, at 120. Administrative decisions are made as a result of consultations with the PAFSC regarding adverse drug reactions. *Id.* The MHLW can suspend the manufacturing or distribution of a drug, recall a drug, revoke approval, change its dosage, and order emergency safety information to be circulated, etc. *Id.* The most frequent type of action taken is requiring notification to health professionals, through revised versions of package inserts. *Id.* The administrative actions performed by the MHLW reflect the information gathered in postmarketing surveillance of drugs. See ENCYCLOPEDIA OF BIOPHARMACEUTICAL STATISTICS 628 (Shein-Chung Chow ed., 2d ed. 2003).

and safety of the drug during a specified period of time after approval.”²³² Under this article, pharmaceutical companies must perform postmarketing surveillance of their drugs within a certain number of years after their approval, to be decided by the MHLW.²³³ Whereas reexamination focuses on ensuring the drug’s level of efficacy, the reevaluation system concentrates on the quality and safety of the drug in the context of current medical and pharmaceutical sciences.²³⁴ The MHLW first selects certain ingredients in drugs to review, and an initial review is performed by the PMDA, who then discusses their data with PAFSC.²³⁵ Once reevaluation has been designated, the PMDA performs the reevaluation and submits their results on the drug’s quality of efficacy and safety to the PAFSC to be published.²³⁶

III. REFORMS

A recent report by current and former members of the FDA’s Drug Safety and Risk Management Advisory Committee pinpoints several flaws of drug regulation.²³⁷ The members called for a “reorganization of the

²³² JPMA, ERITF, *supra* note 207, at 121; see White Paper Report, *supra* note 222 (providing a flow chart of postmarketing surveys in the reexamination and reevaluation process).

²³³ See JPMA, ERITF, *supra* note 207, at 122 (stating that general times for re-examination are 10, 6 and 4-6 years, after approval); see also Neckers, *supra* note 12, at 299 (explaining that the MHLW requires postmarketing re-examination and re-evaluation of all newly approved drugs).

²³⁴ See JPMA, ERITF, *supra* note 207, at 125 (discussing the reevaluation system). See generally Tanaka Katsutoshi, *Problems of Re-evaluation of Drug: Reexamination Systems (Review, Re-evaluation, and GPMSP) of Drug for Medical Use*, 17 CURRENT THERAPY 6, 984-89 (1999), available at <http://scielinks.jp/j-east/article/199921/000019992199A0602967.php> (explaining the history and process of re-evaluation).

²³⁵ See JPMA, ERITF, *supra* note 207, at 131 (charting the reevaluation system); see also, Akira Miyajima, *Role of Japan and Asian Countries in the Global Pharmaceutical Development*, PMDA, Oct. 12, 2006, at 4, <http://www.pmda.go.jp/apec2006ph/presen/1012/03/pdf> (illustrating the operational flow of drug and device development).

²³⁶ See JPMA, ERITF, *supra* note 207, at 131 (graphing the steps in the reevaluation process); Akira, *supra* note 235, at 4 (revealing the overall system and progression of drug and device development).

²³⁷ See generally Furberg et al., *supra* note 117 at 1. The flaws include:

[T]he design of initial preapproval studies lets uncommon, serious adverse events go undetected; massive underreporting of adverse events to the FDA postmarketing surveillance system reduces the ability to quantify risk accurately; manufacturers do not fulfill the majority of their postmarketing safety study commitments; the FDA lacks authority to pursue sponsors who violate regulations and ignore postmarketing safety study commitments; the public increasingly perceives the FDA as having become too close to the regulated pharmaceutical industry; the FDA’s safety oversight structure is suboptimal; and the FDA’s expertise and resources in drug safety and public health are limited.

Id. at 1. The Drug and Safety and Risk Management Drug Advisory Committee’s purpose is to advise the Commissioner regarding responsibilities of making sure drugs are safe for human use, advise on risk management, risk communication, and evaluation of drugs. See FDA, Committee Charter Drug Safety and Risk Management Drugs Advisory Committee, <http://www.fda.gov/>

agency with emphasis on strengthening the evaluation and proactive monitoring of drug safety,” among other things.²³⁸ The first step towards reorganization that the FDA can make is to develop a current set of guidelines and regulations to which drug manufacturers and FDA employees can refer.²³⁹ The FDA has recently taken some initiative in the postmarketing program, yet these newly proposed regulations have not been officially released or published.²⁴⁰ The FDA must promulgate regulatory standards that “provide [the industry] with clearly written, regularly updated documents” in order to encourage compliance.²⁴¹ In comparison to its European and Asian counterparts, the FDA is clearly lacking in this crucial area of pharmacovigilance. Europe’s Volume 9A of the Rules Governing Medicinal Products in the European Union is a complete and updated set of guidelines for postmarketing pharmacovigilance regulation.²⁴² Likewise, Japan’s report from JPMA’s English Regulatory Information Task Force, contains practices and regulations of the pharmaceutical industry that are updated twice a year.²⁴³ In the U.S., the most current guidance on postmarketing safety for drugs is based on regulations that were promulgated in 1997.²⁴⁴ A current set of principles and guidelines for all parties to rely upon will provide the foundation that the FDA needs to emphasize the importance of monitoring drugs.²⁴⁵

Cder/audiences/acspage/DSaRMcharter.htm (last visited Oct. 1, 2008).

²³⁸ Furberg et al., *supra* note 117, at 1.

²³⁹ See Goldman, *supra* note 16, at 514 (“[I]t is incumbent upon national competent authorities to promote regulatory standards that reflect the latest scientific developments, and provide regulated industry with clearly written, regularly updated documents that foster compliance.”); see also Furberg et al., *supra* note 117, at 3 (asserting that the FDA needs to have “additional and clearer authority”).

²⁴⁰ See Goldman, *supra* note 16, at 514 (noting that release of rules and regulations have been delayed); Furberg et al., *supra* note 117, at 1 (asserting that “there has been no meaningful change in our regulatory approach to drug safety during the past decades”).

²⁴¹ Goldman, *supra* note 16, at 514.

²⁴² See *supra* notes 180–204 and accompanying text (describing the breadth and efficiency of Volume 9A).

²⁴³ See generally JPMA, ERITF, *supra* note 207, at iii–vii. The JPMA English Regulatory Information Task force meets twice a year to review any updates in: (1) the “Organization and Function of the Ministry of Health, Labour, and Welfare”; (2) “Pharmaceutical Laws and Regulations”; (3) “Drug Development” Activities by the Industry and their evaluation by the Ministry; (4) “Postmarketing Surveillance of Drugs”; (5) “Dissemination of Drug Information”; and (6) Health Insurance Programs and Drug Pricing.” *Id.*

²⁴⁴ Goldman, *supra* note 16, at 516 (explaining how rules proposed in 2003 have not been finalized and as a result the 1997 rules still govern); see STEPHENS’ DETECTION OF NEW ADVERSE DRUG REACTIONS 433 (John Talbot & Patrick Waller eds., 5th ed. 2004) (stating that the FDA proposed rule changes to the 1997 rules, but those proposed rules have yet to be enacted).

²⁴⁵ See Furberg et al., *supra* note 117, at 1 (noting that there have been only small changes made to the regulatory approach in the past few decades, none of which have changed the status quo in any meaningful way); see also *Further Actions Needed to Improve FDA’s Postmarket Decision-Making Process: Hearing on Drug Safety Before the Subcomm. on Health, Comm. on Energy and Commerce*,

For its next mission, the FDA should focus on improving its monitoring of postmarketing study commitments that drug sponsors agree to conduct.²⁴⁶ Similar to the QPPV in Europe, each drug sponsor should have one executive that is responsible for maintaining a postmarketing system.²⁴⁷ This executive should be held criminally liable for failure to fulfill any of their postmarketing monitoring obligations, as personal responsibility will serve as an incentive for ensuring an effective postmarketing system.²⁴⁸ Also, the FDA must receive more statutory tools for monitoring commitments and ASRs, and for ensuring that commitments are being completed according to schedule.²⁴⁹ Within the past few years, Congress has been pressured to provide the FDA with stronger enforcement tools.²⁵⁰ For failure to complete postmarketing studies within the time specified, The Pharmaceutical Research and Manufacturers Accountability Act of 2005, introduced by Representatives Stark and Berry, proposes fines of up to \$5 million for each month the study remains incomplete.²⁵¹ Because of the FDA's unsubstantiated threat of withdrawal, companies often "drag their feet on studies."²⁵² However, with this bill,

110th Cong. 8 (2007) (statement of Marcia Crosse, Director, Health Care) [hereinafter *Further Actions Needed*] (reporting that the GAO testified that it advised FDA to take steps to make cooperation among regulatory parties easier, and to make the process clearer).

²⁴⁶ See *supra* notes 58–85 and accompanying text (arguing that the postmarket monitoring of prescription drugs by FDA is not as forceful as it should be); see also LESLIE PRAY & SALLY ROBINSON, INST. OF MEDICINE, CHALLENGES FOR THE FDA: THE FUTURE OF DRUG SAFETY 58 (2007) (recommending increased authority so that the FDA can punish drug sponsors who do not cooperate).

²⁴⁷ See *supra* notes 132–133 and accompanying text. Under the current FDA system, the FDA receives reports from several sources and is also required to approve drugs as well, is too complex to effectively monitor. *Id.* In Europe, drug companies each must appoint one person to monitor their drugs postmarket. See *Volume 9A, supra* note 173, at 18.

²⁴⁸ See *supra* notes 132–133 (contending that punishments can serve as an incentive to monitor properly); see also *The European Union Penalties Regulation Explained by Hogan and Hartson Lawyers*, PHARMA MARKETLETTER, July 30, 2007, at 2 (describing the increasing fines that can be levied against drug manufacturers if they do not cooperate).

²⁴⁹ See HHS OIG, *supra* note 42, at 19 (pointing out that the FDA is plagued by vulnerabilities in its ability to monitor drugs postmarket); see also PRAY & ROBINSON, *supra* note 246, at 58 (calling for Congress to increase the strength of the FDA in regard to enforcement of postmarket monitoring).

²⁵⁰ See Steenburg, *supra* note 2, at 367–68 (explaining that the Vioxx saga coupled with the large percentage of ongoing and incomplete studies, may have sparked the need for stronger enforcement tools); see also *Further Actions Needed, supra* note 246, at 9 (recording the GAO's suggestion that Congress expand FDA's enforcement power).

²⁵¹ Steenburg, *supra* note 2, at 368 ("A bill currently pending in the House would allow fines of up to \$5 million, with each thirty-day period constituting a separate violation."); Furberg et al., *supra* note 117, at 2 ("The Pharmaceutical Research and Manufacturers Accountability Act of 2005 (HR 879), introduced by Representatives Stark and Berry, would, if passed, send drug industry CEOs and other executives to jail for a minimum of 20 years if they knowingly conceal serious adverse drug experiences.").

²⁵² Steenburg, *supra* note 2, at 368 (commenting that firms are "inclined to drag their feet" when complying with postmarketing commitments because revocation of approval is rarely exercised, absent a serious safety problem); see 21 U.S.C. § 355(k)(1) (2008) (mandating the terms upon which withdrawal is appropriate).

companies will no longer hesitate to fulfill their commitments in order to avoid liability and fines.²⁵³ The FDA should have legal authority to require industry compliance and completion of postmarketing studies through the use of fines and injunctions.²⁵⁴

Other suggestions for enforcing completion of these studies include: instructing drug applicants to provide additional and meaningful information on their annual status reports, improving their own management information system, and ensuring that FDA reviewers are fulfilling their own responsibilities in overseeing the completion of these commitments.²⁵⁵ Drug applicants should be instructed to include more than just a description and schedule of their commitments.²⁵⁶ Submission of study protocols, completion dates, and final reports can serve as signals that companies have completed one stage and are progressing towards the next.²⁵⁷ A more efficient management system would entail organizing their commitment database by study start dates, original scheduled completion dates, and final report dates.²⁵⁸ Moreover, a system that identifies late ASRs and outstanding commitments would alert reviewers of their status and eliminate the risk of the commitment being overlooked or forgotten.²⁵⁹

²⁵³ See Daniel R. Cahoy, *Medical Product Information Incentives and the Transparency Paradox*, 82 IND. L.J. 623, 653–54 (2007) (noting the Act sought to ensure enforcement of FDA rules by creating serious consequences for manufacturing companies that failed to comply); see also Steenburg, *supra* note 2, at 368 (quoting Representative Pete Stark, as he described the lack of incentives for firms to complete their studies).

²⁵⁴ Kelly, *supra* note 85, at 3 (suggesting the Agency be provided with greater enforcement authority, and that such reinforcement mechanisms “reflect [a] widespread congressional impatience with the fact that the majority of postmarketing surveillance studies promised by companies are never completed”); see Furberg et al., *supra* note 117, at 3 (explaining that for postmarketing studies, the FDA needs additional and clearer authority to hold manufacturers to their commitments and to adherence to a fundamental of sound science that all study results, whether favorable or unfavorable, must be reported to the FDA in a timely manner, accompanied by disclosure to the public and/or other follow-up action; failure to meet postmarketing commitments should have clear consequences for the offenders, which could include fines, probation, public embarrassment, or even drug withdrawal).

²⁵⁵ See HHS OIG, *supra* note 42, at 19–21 (proposing the key changes necessary to ensure a more efficient Agency); see also Gilhooly, *supra* note 49, at 361–62 (stating the Institute of Medicine of the National Academy, in recognizing the drawbacks to the current passive postmarketing system has recommended similar improvements to strengthen FDA authority and promote active surveillance).

²⁵⁶ See HHS OIG, *supra* note 42, 19–20 (arguing the information provided does not assist in ensuring progress of postmarketing commitments); see also GAO, *supra* note 85, at 24 (“Data constraints—such as weaknesses in data sources and limitations in requiring certain studies and obtaining data—contribute to FDA’s difficulty in making postmarket drug safety decisions.”).

²⁵⁷ See HHS OIG, *supra* note 42, at 19–20 (highlighting the importance that the FDA mandate a greater level of detail in ASRs); see also Kelly, *supra* note 85 (commenting that tracking the progress of a company’s postmarketing commitment is a significant issue considering that “about two-thirds of the 1231 studies pending as of September 2005 had not even been initiated”).

²⁵⁸ See HHS OIG, *supra* note 42, at 20 (positing that a more efficient system would ensure the FDA database is populated with useful information); see also Schanz, *supra* note 7, at 496 (stating that the FDA currently lacks a system for managing postmarket study commitments).

²⁵⁹ See HHS OIG, *supra* note 42, at 20 (suggesting that by enhancing the current reporting capability, it would enable reviewers to “readily identify approved new drug applications for which

Timely review of commitment reports and ASRs by FDA reviewers are essential to this process.²⁶⁰ Although the FDA has numerous priorities and a limited staff, postmarketing commitments must be accurately and promptly monitored.²⁶¹

Another key improvement involves the FDA's Adverse Event Reporting System (AERS). The FDA must shift from passive surveillance of adverse events to proactive surveillance.²⁶² One method is to have trained employees who specifically search for adverse events to add to an existing adverse events database.²⁶³ Implementing a systematic solicitation of care providers for adverse event reports, and a systematic screening of those records will provide for greater coverage of adverse events.²⁶⁴ A systematic collection of primary patient records will also yield better results.²⁶⁵ Another proactive method is for Congress to allow the FDA access to large, private and public administrative databases such as the Department of Veterans Affairs, and the Department of Defense, as well as other large health plans.²⁶⁶ This would allow the FDA to provide important safety information by linking pharmacy databases with clinical patient

ASRs are due as well as those with open commitments that are behind schedule"); *see also* Schanz, *supra* note 7, at 496–97 (explaining that one-third of annual status reports on postmarketing commitments are not submitted or are incomplete, and even many completed reports lack useful information).

²⁶⁰ *See* HHS OIG, *supra* note 42, at 21 (positing that in doing so, it will allow the public and medical community to be aware of the risks, benefits, and optimal uses of approved drugs); *see also* Steenburg, *supra* note 2, at 326–27 (explaining that given the potential adverse effects on American patients and the absence of absolute certainty as to all the risks associated with a drug at the time of approval, the timeliness of completing postmarketing commitments may be critical to the public safety).

²⁶¹ *See* HHS OIG, *supra* note 42, at 21 (stating FDA must find a way to provide the information, tools, and time to its employees to complete the postmarketing studies); *see also* Basquill, *supra* note 1, at 84 ("[F]or all their responsibility, the FDA is woefully understaffed and under-funded.").

²⁶² *See* Furberg et al., *supra* note 117, at 4 (advocating that a switch to active surveillance approach would be more beneficial than the passive approach); *see also* Gilhooly, *supra* note 49, at 361–62 (stating that the first step in detecting adverse effects is to implement an active surveillance system).

²⁶³ *See* Bright, *supra* note 11, at 611 (suggesting an employee could systematically solicit care providers, screen records for evidence of adverse effects, or download primary patient records); *see also* Denise Grady, *Medical Journal Calls for New Drug Watchdog*, N.Y. TIMES, Nov. 23, 2004, at A1 (arguing that the problem with current drug tracking is that it is done by drug makers rather than independent parties).

²⁶⁴ *See* Bright, *supra* note 11, at 611–12 (stating that other writings have found that soliciting the information has produced more reports than routine reporting systems); *see also* Gilhooly, *supra* note 49, at 363 (discussing Congress' goal of covering 100,000,000 patients' records by 2012 through the active surveillance system).

²⁶⁵ *See* Bright, *supra* note 11, at 611–612 (noting findings that show solicitation revealed significant numbers that were not found through other means). *See generally* Neckers, *supra* note 12, at 303 (positing that increased reporting and vigilance will lead to decreases in drug related injuries).

²⁶⁶ *See* Furberg et al., *supra* note 117, at 4 (suggesting that Congress provide additional money and staff for the FDA to utilize these databases); *see also* Gilhooly, *supra* note 49, at 370 (stating that the law requires the FDA to publish postmarket safety information on a website to better inform patients and care providers of drug risks).

information.²⁶⁷ The FDA could also implement a surveillance system based on large population-based and disease-specific registries from other countries.²⁶⁸ For example, common conditions that occur internationally, such as liver or renal failure, or sudden cardiac death, could be the focus of these disease-specific registries.²⁶⁹ The FDA's ideal surveillance program "should be based on epidemiologic principles so that inferences can be made about the specific, overall, and relative public health burdens of different types of ADE."²⁷⁰

Other possible reforms are to implement a policy of "conditional approvals," or to create a system of scheduled reviews, such as those in Japan.²⁷¹ Under conditional approvals, a drug would have a time-limited approval status, conditioned on their completion of recommended and requested postmarketing studies.²⁷² For example, a study that leads to approval might include 500 patients, but 5000 might be needed to judge safety. "Conditional approval might be based on 500 patients, and the company might be told that data on 5000 will be required for full approval."²⁷³ If a drug remains "conditionally approved until certain data are available, providing an incentive to collect those postmarketing data" can be another alternative.²⁷⁴ The EMEA is currently attempting to make a "1-year conditional approval a regulatory option."²⁷⁵ Adopting Japan's

²⁶⁷ See Furberg et al., *supra* note 117, at 4 (positing that the FDA should routinely review drug withdrawals to find connections); see also Gilhooly, *supra* note 49, at 363 (noting that the FDA is taking steps to link the information from Medicare and private insurance companies to its own database).

²⁶⁸ Furberg et al., *supra* note 117, at 4 (suggesting that the overrepresentation of suspected drugs in disease-specific databases would point to potential for harmful drug effects); see also Bright, *supra* note 11, at 611 (discussing registries set up in the United Kingdom to monitor adverse affects of specific drugs).

²⁶⁹ Furberg et al., *supra* note 117, at 4 (adding that international disease-specific registries would nicely complement the FDA's MEDWatch program); see Neckers, *supra* note 12, at 304 (discussing the AERS which stores various information on the safety of FDA-approved drugs).

²⁷⁰ Bright, *supra* note 11, at 605.

²⁷¹ See Furberg et al., *supra* note 117, at 4 (suggesting that "[f]irst, the FDA should have a 'conditional approval' policy for new drugs"). See generally John R. Manthei et al., *Changing the Landscape for Device Manufacturers: Medical Device User Fee and Modernization Act of 2002*, 15 NO. 2 HEALTH LAW. 10, 11 (2002) (describing the Medical Device User Fee and Modernization Act of 2002 which "imposes stronger pre-market and post-market controls on reprocessed medical devices that are approved or cleared for single-use only").

²⁷² See Furberg et al., *supra* note 111, at 4 ("A time-limited, conditional approval status would place pressure on the sponsors to conduct and report recommended safety studies."); see also Kelly, *supra* note 85 ("[T]he IOM wants Congress to give the FDA legal authority to require industry compliance with FDA-initiated changes in labeling and completion of postmarketing studies, to limit distribution of certain new drugs, to restrict direct to consumer (DTC) advertising for a period after a new drug is launched, and to maintain 'an active adverse event surveillance system.'").

²⁷³ See Kelly, *supra* note 85.

²⁷⁴ Furberg et al., *supra* note 111, at 4.

²⁷⁵ *Id.*

systematic reviews of drugs a certain number of years after approval are another way of closely monitoring for adverse events.²⁷⁶ The FDA's "system consists mainly of pharmaceutical companies' reports of adverse drug reactions and adverse events."²⁷⁷ However, a postmarketing system with more precautionary phases like Japan's system, would create a more effective and successful system.²⁷⁸

CONCLUSION

The FDA has enormous responsibilities concerning the approval and testing of every drug before it is released onto the market. The FDA undoubtedly continues to make valuable reforms to its drug approval process. However, the monitoring of a drug's safety and efficacy after approval is just as important. As the international leader in the pharmaceutical market, it is imperative that the United States maintains an efficient process of regulating drugs post-approval that keeps pace with the ever-changing pharmaceutical world. The persisting problems with postmarketing must be dealt with immediately and innovatively – whether this requires using fines and injunctions as a way of creating incentive, or emulating other countries that have successfully handled similar problems. Nevertheless, these problems must be resolved.

²⁷⁶ See *supra* notes 179–183 and accompanying text (describing the workings of Japan's monitoring system); see also Yahiro & Nakai, *supra* note 205 (providing information regarding the newly revised Japanese pharmaceutical laws).

²⁷⁷ Neckers, *supra* note 12, at 308.

²⁷⁸ See Neckers, *supra* note 12, at 308 (noting that in Japan, the postmarketing surveillance system requires pharmaceutical companies to complete early adverse reaction reports, clinical experience investigation, special investigations, and postmarketing clinical studies); see also Yahiro & Nakai, *supra* note 205 (revealing that the Japanese government "enacted sweeping revisions of the Pharmaceutical Affairs Law (PAL)" on July 31, 2002, which "reflect the government's efforts to ensure the quality, safety, and efficacy of medical products").

