

# FOOD AND DRUG LAW JOURNAL

*Analyzing the Laws, Regulations, and Policies  
Affecting FDA-Regulated Products*

Postmarket Surveillance

## Postmarketing Pharmacovigilance Compliance in the Midst of Regulatory Uncertainty

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VOLUME 62 NUMBER 3 2007

# U. S. Postmarketing Pharmacovigilance Compliance in the Midst of Regulatory Uncertainty

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## I. INTRODUCTION

In the United States, heightened concern about safe use of such marketed medical products as prescription and non-prescription drugs, biologics and medical devices has been manifest for the past several years. As a result, the methods by which the relative benefit/risk balance of medical products are assessed, monitored and acted upon have come under intense public, congressional and legal scrutiny. This attention is not unprecedented, but the sustained focus on the Food and Drug Administration's (FDA's) Center for Drug Evaluation and Research (CDER) has called into question the effectiveness of what traditionally has been one of the most trusted federal agencies in the United States.

At the same time, public perception as to the pharmaceutical industry's stated commitment to safety is clearly at low ebb. In its January 2007 article "Recapturing the Vision: Restoring Trust in the Pharmaceutical Industry by Translating Expectations into Actions," PricewaterhouseCoopers reported that a nationwide survey of consumers and industry stakeholders (e.g., physicians, health insurers, researchers) found public belief that the industry's priority is profits before patients.<sup>1</sup> This result, along with their additional finding that the public disregards the significant benefits pharmaceutical companies bring to healthcare, provides a cautionary note to the industry.

That a significant proportion of our fellow citizens think neither the governmental agency charged to protect their health, nor the industry in business to discover and produce products advantageous to treatment of their illnesses, are performing their jobs adequately is sobering indeed. In particular, for medical product safety specialists at FDA or those working in the pharmaceutical industry (or individuals with such experience), it can be discouraging to find that one's efforts in service of public health appear to foster little respect or appreciation.

These negative views seem to be at variance with the impact of multinational initiatives conducted under the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use auspices, which along with Council for International Organizations of Medical Sciences (CIOMS) projects and other advances have invigorated pharmaceutical safety into a global endeavor intended to protect public health, not hinder it. The new paradigm of medical product safety as a continuum that starts with preclinical testing, continues throughout human premarketing clinical trials and then market approval, and which necessitates ongoing surveillance and constant reevaluation of a product's benefit-risk balance throughout its life cycle, should also serve to enhance safe use.

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<sup>1</sup> Consumers and Pharmaceutical Companies Far Apart on Views of Pharma Industry, Finds PricewaterhouseCoopers Survey, available at [www.pwc.com/servlet/pwcPrintPreview?LNLLoc=/extweb/npressrelease.nsf/docid/DA82FDA0939ACD99852572600056DF67](http://www.pwc.com/servlet/pwcPrintPreview?LNLLoc=/extweb/npressrelease.nsf/docid/DA82FDA0939ACD99852572600056DF67).

However, even with promising new clinical pharmacological, pharmacogenomic and epidemiological techniques at our disposal, the acknowledged limitations of premarketing clinical trials (relatively short duration; narrow population; narrow indications; relatively small size) remain daunting obstacles to overcome with respect to the safety of products as they emerge onto the market.<sup>2</sup> Just as formidable are the complexities of risk communication and risk management in the postmarketing realm, with programs intended to mitigate known risks achieving varying degrees of success or failure.<sup>3</sup>

Both considerations of public health, and the litigious, risk-adverse medicolegal and societal environment in the United States, mandate that companies do their utmost to ensure that their processes and procedures for performing premarketing clinical safety and postmarketing pharmacovigilance are both in compliance with regulatory requirements and designed to utilize state-of-the-art methods. Companies have learned to look beyond strictly local (i.e., national) regulatory requirements in establishing compliance processes and procedures that meet the demands of the new international paradigm.<sup>4</sup>

For their part, it 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.

It should thus follow that the ongoing investigation of FDA's postmarketing drug safety program include assessment as to whether this indeed is happening—however, that has clearly not been the case.

Despite multiple congressional inquiries, Government Accountability Office (GAO) evaluation, Institute of Medicine (IOM) study, hearings on the fourth iteration of the Prescription Drug User Fee Act (PDUFA IV) and numerous articles in the press and scientific literature, little if any emphasis has been placed on the critical role of FDA's inspectional programs that monitor compliance with pharmaceutical adverse event reporting requirements, nor on ongoing delays in finalization and release of needed rules, regulations and guidances related to drug safety. If appraisal of pharmaceutical safety in the United States is to be truly complete, appropriate attention must be paid to these vital aspects, and the input of those specializing in premarketing clinical safety and postmarketing pharmacovigilance actively sought.

In order to examine these crucial public health issues, the current status of significant safety-related FDA documents, concomitant repercussions that have already been felt due to the regulatory lag, and postmarketing pharmacovigilance inspections in the United States and the European Union (EU) will be reviewed.

## II. HISTORICAL PERSPECTIVE AND CURRENT REGULATIONS

Given the prominence of FDA's position in pharmaceutical safety and innovative medical product risk management, a historical perspective on both the agency's national and cooperative international programs is important to understanding current regulatory circumstances.

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<sup>2</sup> Stephen A. Goldman, Dianne L. Kennedy & Ronald Lieberman (editors), *Clinical Therapeutics and the Recognition of Drug-Induced Disease (MedWatch Continuing Education Article)*, Food and Drug Administration, Rockville, MD. (June 1995), available at [www.fda.gov/medwatch/articles/dig/rcontent.htm](http://www.fda.gov/medwatch/articles/dig/rcontent.htm).

<sup>3</sup> Stephen A. Goldman, *Communication of Medical Product Risk: How Effective is Effective Enough?*, 27 *Drug Safety* 519-534 (2004).

<sup>4</sup> Stephen A. Goldman, *Auditing Safety-Related Processes and Procedures: Lessons Learned for Global Compliance and Quality*, 40 *DRUG INFORMATION JOURNAL* 165-175 (2006).

### A. *FDA Regulations and Guidances for Pre- and Postmarketing Safety Reporting for Human Drugs and Biologics*

Beginning in 1990, FDA embarked on a major initiative to clarify and revise its regulations regarding pre- and postmarketing safety reporting for human pharmaceuticals. The agency issued several rules and guidance documents in this effort, including:

- **October 1994:** proposed rulemaking, with proposed changes to pre- and postmarketing expedited reporting of adverse experiences (AEs) based on ICH E2A “Clinical Safety Data Management: Definitions and Standards for Expedited Reporting” guideline<sup>5</sup> and postmarketing periodic reporting [Periodic Safety Update Reports (PSURs)] based on CIOMS II<sup>6</sup>
- **July 1997:** removal of requirement to submit Increased Frequency Reports on an expedited basis
- **August 1997:** release of guidance, “Postmarketing Adverse Experience Reporting for Human Drug and Licensed Biological Products—Clarification of What to Report,”<sup>7</sup> based on ICH E2A
- **October 1997:**
  - Finalized pre- and postmarketing expedited reporting of AEs proposed in October 1994
  - Announced delay in finalization of October 1994 PSUR-related proposals, pending FDA consideration of ICH recommendations (E2C guideline)<sup>8</sup>
- **March 2001:** Release of draft guidance, “Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines”<sup>9</sup>:
  - Revised earlier guidances based on July 1997 and October 1997 rulemaking
  - Provided clarification for certain reporting requirements (e.g., Day 0; “identifiable patient;” follow-up reports)
  - When finalized, will replace three previous guidances [in addition to August 1997 guidance listed above, “Guideline for Postmarketing Reporting of Adverse Drug Experiences”<sup>10</sup> (March 1992) and “Guideline for Adverse Experience Reporting for Licensed Biological Products”<sup>11</sup> (October 1993)].

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<sup>5</sup> International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, Guideline E2A: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting, Step 4 version (Oct. 29, 1994), available at [www.ich.org/LOB/media/MEDIA436.pdf](http://www.ich.org/LOB/media/MEDIA436.pdf).

<sup>6</sup> CIOMS II Working Group, International Reporting of Periodic Drug-Safety Update Summaries, Council For International Organizations Of Medical Sciences, Geneva, Switzerland (1992).

<sup>7</sup> FDA, Postmarketing Adverse Experience Reporting for Human Drug and Licensed Biological Products—Clarification of What to Report (guidance) (Aug. 1997), available at [www.fda.gov/cder/guidance/1830fn1.pdf](http://www.fda.gov/cder/guidance/1830fn1.pdf).

<sup>8</sup> ICH of Technical Requirements for Registration of Pharmaceuticals for Human Use, Guideline E2C: Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs, Step 5 version (Nov. 1996), available at [www.fda.gov/cder/guidance/1351fn1.pdf](http://www.fda.gov/cder/guidance/1351fn1.pdf).

<sup>9</sup> FDA, Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines (draft guidance) (Mar. 2001), available at [www.fda.gov/medwatch/report/guide2.htm](http://www.fda.gov/medwatch/report/guide2.htm).

<sup>10</sup> FDA, Guideline for Postmarketing Reporting of Adverse Drug Experiences (Mar. 1992), available at [www.fda.gov/cder/guidance/old037fn.pdf](http://www.fda.gov/cder/guidance/old037fn.pdf).

<sup>11</sup> FDA, Guideline for Adverse Experience Reporting for Licensed Biological Products (Oct. 1993).

Of particular note, the 2001 draft guidance is intended to assist applicants and other responsible parties in fulfilling FDA's existing postmarketing safety reporting requirements for human marketed drug and biological products (21 CFR 310.305, 314.80, 314.98, 600.80, and 600.81.2). Further, it states that once FDA has finalized proposed rules that amend these existing regulations, including revisions based on ICH guidelines and mandating both PSURs and electronic reporting of postmarketing safety reports, the draft guidance, as finalized, will be updated to assist industry in complying with the new safety reporting requirements.<sup>12</sup>

However, the 2003 "Safety Reporting Requirements for Human Drug and Biological Products: Proposed Rule"<sup>13</sup> (2003 Proposed Rule) is not yet final. As a result, the most current guidance on postmarketing safety reporting on human pharmaceuticals in the United States is more than six years old, and applies to regulations finalized in 1997. Further, the guidance is still in draft.

### B. Task Force on Risk Management

In 1998, under then Commissioner Dr. Jane Henney, a Task Force was established to assess the system for managing risks associated with the use of FDA-approved medical products, with particular focus on FDA's role. With regard to the agency's role, the Task Force was asked to concentrate on three basic areas:

- Quality of FDA's premarketing review and risk assessment;
- Strengths and weaknesses of FDA's postmarketing surveillance and risk assessment;
- Other FDA risk assessment activities;

The resulting May 1999 Report to the FDA Commissioner, "Managing the Risks from Medical Product Use: Creating a Risk Management Framework,"<sup>14</sup> was a landmark document that established FDA's philosophy in this regard.

In combination with international safety-related initiatives under ICH (e.g., E2A Guideline)<sup>15</sup> and CIOMS (e.g., CIOMS IV: *Benefit-Risk Balance for Marketed Drugs: Evaluating Safety Signals*),<sup>16</sup> the Task Force Report provided a framework for FDA's ongoing programs and initiatives for safe use of medical products with both national and global applicability.

The Task Force recognized that evaluation of medical product risk management entailed assessment within the entire healthcare delivery system, and thus examined all FDA risk management activities in this context.<sup>17</sup> Adapting a federal proposed risk management model for specific health hazards,<sup>18</sup> the Task Force assessed FDA's role in both the premarketing and postmarketing phases.

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<sup>12</sup> 2001 Postmarketing Safety Reporting Draft Guidance, *op. cit.*, at 4.

<sup>13</sup> Department of Health and Human Services (HHS), FDA, Safety Reporting Requirements for Human Drug and Biological Products (proposed rule), 68 *Federal Register* 12406-12497 (2003), available at [www.fda.gov/OHRMS/DOCKETS/98fr/03-5204.pdf](http://www.fda.gov/OHRMS/DOCKETS/98fr/03-5204.pdf).

<sup>14</sup> Task Force on Risk Management, Report to the FDA Commissioner: Managing the Risks from Medical Product Use: Creating a Risk Management Framework. HHS, FDA, Rockville, MD, (May 1999), available at [www.fda.gov/oc/tfrm/riskmanagement.pdf](http://www.fda.gov/oc/tfrm/riskmanagement.pdf).

<sup>15</sup> ICH E2A Guideline, *op. cit.*

<sup>16</sup> CIOMS IV Working Group, *Benefit-Risk Balance for Marketed Drugs: Evaluating Safety Signals*. Council For International Organizations Of Medical Sciences, Geneva, Switzerland (1998).

<sup>17</sup> Task Force on Risk Management, *op. cit.*, at 1.

<sup>18</sup> Presidential/Congressional Commission on Risk Assessment and Risk Management, *Framework for Environmental Health Risk Management—Final Report, Volume 1* (1997).

Seeing the need for a new systems framework for risk management, the Task Force posited that better risk understanding combined with greater system integration would result in more effective risk interventions.

The Task Force assigned medical product risks to four general categories: 1) known side effects (from which most injuries and deaths result, an appreciable number avoidable);<sup>19</sup> 2) medication/medical device errors (also preventable); 3) product defects (uncommon in the United States); and 4) remaining uncertainties. Regarding FDA's role in risk management, it was found that safety-based drug withdrawals rates had remained essentially unchanged over decades, unexpected serious adverse events leading to labeling changes were occurring less frequently than before, and postmarketing surveillance/risk assessment was performing as intended. Discovery of adverse events in premarketing was recognized as limited by several known factors inherent to the process, and that changes would increase costs and slow availability of new agents.

Most of the Task Force recommendations focused on ways to further improve risk management within the existing FDA structure (e.g., heightening surveillance of products new to the market). Options to address known limitations of premarketing study (e.g., large simple trials) were suggested, while other recommendations included enrichment of FDA's role and responsibilities in risk communication.

The Task Force made it clear that the responsibility for risk management of medical products used in the United States does not rest solely with FDA, but rather is shared by the agency with industry, health professionals, patients, other federal groups, healthcare delivery systems, and professional organizations.<sup>20</sup>

The Task Force report had a decided impact on FDA's risk management programs that is evident in regulatory actions taken in relation to marketed pharmaceuticals used unsafely (e.g., co-prescription of known contraindicated drugs)<sup>21</sup> and the underlying philosophy of the 2003 Proposed Rule. Whether it had any effect outside the United States is unclear—the 2001 Summary Report of the Heads of Agencies Ad Hoc Working Group, “Establishing A European Risk Management Strategy,” barely mentioned the Task Force report, but did manifest similar concerns and provided recommendations for how to enhance public health in relation to risks associated with medication use.<sup>22</sup>

### III. 2003 SAFETY REPORTING REQUIREMENTS FOR HUMAN DRUG AND BIOLOGICAL PRODUCTS: PROPOSED RULE

In March 2003, FDA released its proposed rule on safety reporting requirements for human drug and biological products, which had been several years in the making. Encompassing both premarketing (21 CFR 312.32) and postmarketing (21 CFR 310.305, 314.80, 314.98 and 600.80) safety reporting regulations, its stated goals were to:

- Harmonize with ICH and CIOMS standards;
- Enhance “worldwide consistency” in safety data collection and safety report submission;

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<sup>19</sup> David W. Bates, Lucian L. Leape & Stephen Petrycki, *Incidence and Preventability of Adverse Drug Events in Hospitalized Adults*, 8 JOURNAL OF GENERAL INTERNAL MEDICINE 289-294 (1993).

<sup>20</sup> Task Force on Risk Management, *op. cit.*, at 3-5.

<sup>21</sup> Stephen A. Goldman, *Drug Safety* (2004), *op. cit.*

<sup>22</sup> Summary Report of The Heads of Agencies Ad Hoc Working Group. Establishing a European Risk Management Strategy (Jan. 2003), available at [www.hma.eu/uploads/media/ERMS\\_summary\\_report.pdf](http://www.hma.eu/uploads/media/ERMS_summary_report.pdf).

- Improve safety report quality;
- Speed evaluation of important safety information by agency; and
- Protect/promote public health.<sup>23</sup>

While it is beyond the scope of this paper to summarize the entire document, specific aspects of the Proposed Rule bear examination in context of the current scrutiny of the FDA postmarketing surveillance program for pharmaceuticals.

### A. *Causality Determination: Clinical Trials*

Under the Proposed Rule, the current regulatory definitions of “associated with the use of the drug” and “adverse drug experience” would be changed to “suspected adverse drug reaction (SADR).” For biologics, “adverse experience” would be changed to “suspected adverse reaction (SAR).” In further regard, SADR is defined as:

A noxious and unintended response to any dose of a drug [“biological” for proposed 600.80(a)] product for which there is a reasonable possibility that the product caused the response. In this definition, the phrase “a reasonable possibility” means that the relationship cannot be ruled out.<sup>24</sup>

FDA recognized that with respect to clinical studies of investigational and marketed pharmaceuticals, this proposed definition is likely to result in increased safety reporting to FDA from some studies, as “reasonable possibility” would now be specifically defined. Under this proposed definition, an SADR seen as unlikely or remotely related to study product would still need to be reported (as opposed to the typical interpretation of current regulatory requirements).

To alleviate possible SADR “over-reporting” in studies of patients with serious, potentially fatal diseases (e.g., cancer), FDA invited proposals for alternative(s) ways to handle SADR reporting in such cases, in order to minimize “over-reporting” of uninformative events while insuring reporting of relevant unexpected events.<sup>25</sup>

The Proposed Rule’s definition of “reasonable possibility,” as FDA pointed out, is consistent with that included in the E2A definition for Adverse Drug Reaction (ADR). Notwithstanding, it would likely result in a significant change in U.S. safety reporting for clinical studies, and would also be inconsistent with the European definition. As stated in the Detailed Guidance on the Collection, Verification and Presentation of Adverse Reaction Reports Arising from Clinical Trials on Medicinal Products for Human Use regarding assessment of causality, “All adverse events judged by either the investigator or the sponsor as having a reasonable suspected causal relationship to an investigational medicinal product qualify as adverse reactions,” with “reasonable causal relationship mean[t] to convey in general that there is evidence or argument to suggest a causal relationship.”<sup>26</sup>

As a result, it is entirely possible that a serious, unexpected adverse event arising in clinical trials would be reported on an expedited basis in the United States if a

<sup>23</sup> 2003 Proposed Rule, *op. cit.*, at 12406.

<sup>24</sup> 2003 Proposed Rule, *Id.*, at 12417.

<sup>25</sup> 2003 Proposed Rule, *Id.*, at 12418.

<sup>26</sup> European Commission Enterprise Directorate-General, Detailed Guidance on the Collection, Verification and Presentation of Adverse Reaction Reports Arising from Clinical Trials on Medicinal Products for Human Use, *available at* [www.ottosen.com/clinicaltrials/regulations/guidance%20on%20clinical%20trial%20reporting%20EU%20CT3Rev1.pdf](http://www.ottosen.com/clinicaltrials/regulations/guidance%20on%20clinical%20trial%20reporting%20EU%20CT3Rev1.pdf).

relationship between the medicinal product and event can not be ruled out, but the same event would not be so reported in the EU if it was judged by the investigator and sponsor that insufficient evidence existed to suggest a causal relationship. Such inconsistency would be of significant concern from clinical safety, regulatory, statistical and data management standpoints.

### B. *Causality Determination: Postmarketing*

As FDA makes clear, the proposed change of “adverse drug experience” to “SADR” would not affect safety reporting from spontaneous sources, as every spontaneous report currently must be submitted to FDA regardless of whether the manufacturer or applicant considers it to be drug related. This would continue under the Proposed Rule, which states that “the applicant must always assume, for safety reporting purposes under this section, that there is at least a reasonable possibility, in the opinion of the initial reporter, that the drug [biological] product caused the spontaneously reported event.”<sup>27</sup>

This is at some variance with the recently finalized Volume 9A of the Rules Governing Medicinal Products in the European Union: Guidelines on Pharmacovigilance for Medicinal Products for Human Use, which states:

Spontaneous reports of adverse reactions received from Healthcare Professionals should be reported by the Marketing Authorisation Holder (MAH) if:

- the Healthcare Professional has made a statement that a causal relationship between the event and the medicinal product is considered to be at least a reasonable possibility; or if
- the Healthcare Professional has not made any statement on the suspected causal relationship or has stated that the causal relationship is unknown; or if
- the Marketing Authorisation Holder considers that a causal relationship is at least a reasonable possibility.

If the Healthcare Professional has made an explicit statement that a causal relationship between the medicinal product and reaction has been excluded and the Marketing Authorisation Holder agrees with this, the event should not be reported.<sup>28</sup>

Thus, as is the case with clinical trial adverse events, it is entirely possible that a serious, unexpected spontaneously reported adverse event reported on an expedited basis in the United States would not be so reported in the EU if the reporter specifically states that a causal relationship has been excluded, and the MAH agrees.

### C. *Information to be Reported on an Expedited Basis*

Under the Proposed Rule, in addition to serious, unexpected SADRs, a clinical trial sponsor would have to notify FDA and all investigators of information that “based on appropriate medical judgment, might materially influence the benefit-

<sup>27</sup> 2003 Proposed Rule, *op. cit.*, at 12478.

<sup>28</sup> European Commission, Volume 9A of the Rules Governing Medicinal Products in the European Union: Guidelines on Pharmacovigilance for Medicinal Products for Human Use, 54 (Apr. 2007), available at <http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev9.htm>.

risk assessment of an investigational drug or that would be sufficient to consider changes in either product administration or in the overall conduct of a clinical investigation”<sup>29</sup> within 15 calendar days. This would encompass significant unexpected *in vitro*, animal or human (clinical; epidemiological) study safety findings or aggregate data from studies suggesting significant risk to humans (e.g., mutagenicity, teratogenicity or carcinogenicity).

In a similar vein, the Proposed Rule would not only maintain currently mandated expedited submission of serious, unexpected spontaneous reports and associated follow-up information within 15 calendar days, but would also require expedited reporting of information sufficient to consider changes in administration of a pharmaceutical, based on appropriate medical judgment, that encompasses the same categories of data as for clinical trials.

There are other requirements for postmarketing data review and expedited reporting under the Proposed Rule, including:

*Review of Safety Information:* each applicant with an approved NDA must “promptly review all safety information pertaining to its product obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from commercial marketing experience, postmarketing clinical investigations, postmarketing epidemiology/surveillance studies, animal or *in vitro* studies, electronic communications with applicants via the Internet (e.g., e-mail), reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities that have not been previously reported to FDA by the applicant.”<sup>30</sup>

This change is very much in keeping with the Task Force Report, and the concept of ongoing assessment of a pharmaceutical’s benefit-risk profile based on incoming information. It is also consistent with Volume 9A.

“*Always Expedited Reports*”: these are medically significant SADR that must be reported on an expedited basis, regardless of expectedness and whether the SADR leads to a serious outcome:

- Congenital anomalies;
- Acute respiratory failure;
- Ventricular fibrillation;
- Torsades de pointe ;
- Malignant hypertension;
- Seizure;
- Agranulocytosis;
- Aplastic anemia;
- Toxic epidermal necrolysis;
- Liver necrosis;
- Acute liver failure;
- Anaphylaxis;
- Acute renal failure;
- Sclerosing syndromes;
- Pulmonary hypertension; and
- Pulmonary fibrosis”

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<sup>29</sup> 2003 Proposed Rule, *op. cit.*, at 12476.

<sup>30</sup> 2003 Proposed Rule, *Id.*, at 12478.

- “Confirmed or suspected transmission of an infectious agent by a marketed drug or biological product,”
- “Confirmed or suspected endotoxin shock,”
- “Any other medically significant SADR that FDA determines to be the subject of an always expedited report (i.e., may jeopardize the patient and/or require medical or surgical intervention to treat the patient or subject).”<sup>31</sup>

This concept is consistent with CIOMS V’s recommendation that in view of the lack of objective standards for what constitutes an *important medical event*, companies could use a list of terms for what constitutes a serious AE (with the caveat that no such list should substitute for medical judgment applied to any individual case).<sup>32</sup> It is also consistent with past pharmacovigilance experience that accumulation of cases involving a serious AE, even if well-known, can provide further information that is of significant clinical value (e.g., epidural or spinal hematomas with the concurrent use of low molecular weight heparins/heparinoids and spinal/epidural anesthesia or spinal puncture).<sup>33</sup>

In its response to the Proposed Rule, the Pharmaceutical Research and Manufacturers of America (PhRMA) stated that it was “sympathetic to the idea that for certain events, due to their nature or severity, a standard list might be useful that would characterize such events as ‘always serious’ but not ‘always expedited.’ We question the value of submitting expedited reports for expected SADRs, already described in labeling, information FDA will always receive in periodic submissions.”<sup>34</sup>

*Medication Errors (Actual/Potential) Occurring in U.S.:* Both actual and potential medication error reports from inside the U.S., irrespective of whether they result in a serious SADR, non-serious SADR, or no SADR, are to be reported on a 15-day expedited basis under the Proposed Rule. These include medication errors that were prevented before the product was actually administered and potential medication errors that do not involve a patient (i.e., information/complaint about similarities in product name, packaging or labeling).<sup>35</sup>

In its response, PhRMA stated that while it recognized “the importance of monitoring for, understanding, and preventing medication errors, it questions the basis for introducing what we believe to be excessively demanding new requirements, including expedited reporting of ‘actual and potential’ cases. The new requirements would strangely hold medication errors to a higher regulatory standard than even serious suspected ADRs.”<sup>36</sup>

As to Volume 9A, it is stated that the MAH should:

report cases of medication errors that are associated with serious adverse reactions on an expedited basis in accordance with the requirements in Chapter I.4, and as required by national requirements. Cases not associated with adverse reactions and near misses should only be reported in accordance with national requirements. Cumulative information on

<sup>31</sup> 2003 Proposed Rule, *Id.*, at 12479.

<sup>32</sup> CIOMS Working Group V, *Current Challenges in Pharmacovigilance: Pragmatic Approaches*, Council for International Organizations of Medical Sciences, Geneva, Switzerland (2001).

<sup>33</sup> FDA, Q & A’s: Low Molecular Weight Heparins/ Heparinoids and Spinal/Epidural Anesthesia (May 6, 1998), available at [www.fda.gov/medwatch/SAFETY/1998/lovq&a.htm](http://www.fda.gov/medwatch/SAFETY/1998/lovq&a.htm).

<sup>34</sup> PhRMA (Alan Goldhammer), *Comments on Safety Reporting Requirements for Human Drug and Biological Products*; Proposed Rule, 23 (Oct. 14, 2003), available at [www.fda.gov/ohrms/dockets/dailys/03/oct03/101403/00n-1484-c000028-vol4.pdf](http://www.fda.gov/ohrms/dockets/dailys/03/oct03/101403/00n-1484-c000028-vol4.pdf).

<sup>35</sup> 2003 Proposed Rule, *op. cit.*, at 12422.

<sup>36</sup> *Id.* at 8.

medication errors, resulting in adverse reaction or not, should be discussed in the section of the Periodic Safety Update Report on the overall safety evaluation.<sup>37</sup>

The Proposed Rule medication error requirements were based on increased study and accruing knowledge, including recognition and evaluation of potential medication errors, followed by appropriate remedial action, which can serve to prevent occurrence of actual patient harm. More than 5,000 error reports were filed with FDA during 1993-1998, 18 percent of which were reported directly through the voluntary MedWatch program, and 82 percent from manufacturers;<sup>38</sup> another study showed that four reports classified as potential errors received by FDA (noting "small print size" and "confusing label") lead to labeling revisions in an effort to minimize user error.<sup>39</sup>

#### D. Other Requirements

*Full Data Set:* The Proposed Rule acknowledges that the *minimum data set* (identifiable patient, identifiable reporter, suspect drug/biological product and SADR) constituting a report by themselves is generally not sufficient for quality pharmacovigilance on serious SADRs. Completion of "all applicable elements" on the 3500A or CIOMS I forms, "including a concise medical narrative of the case (i.e., an accurate summary of the relevant data and information pertaining to an SADR or medication error)"<sup>40</sup> is thus stipulated.

*Active Query:* In the same vein, a healthcare professional ("e.g., physician, physician assistant, pharmacist, dentist, nurse, any individual with some form of healthcare training")<sup>41</sup> representing the manufacturer or applicant is required to speak directly to an initial SADR or medication error reporter if the outcome or minimum data set was not determinable on first receipt of the report. Active query, as discussed in the Proposed Rule, "entails, at a minimum, a focused line of questioning designed to capture clinically relevant information associated with the drug product [licensed biological product ...] and the SADR ..."<sup>42</sup>

*PSURs:* In a major change, PSURs, rather than traditional periodic safety reports (TPSRs), were to be required for products approved for marketing on or after January 1, 1998. The proposed new submission schedule (as opposed to the current periodicity of TPSRs, is as follows:

- Two years after United States approval: semiannually (every six months);
- Next three years: annually; and
- Every five years thereafter.

The details regarding PSURs under the Proposed Rule are beyond the scope of this article. However, it is worth noting that non-serious expected SADRs are to be excluded from PSURs (except for those involving vaccines), while foreign

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<sup>37</sup> Volume 9A, *op. cit.*, at 66.

<sup>38</sup> Jerry Phillips, Sammie Beam, Allen Brinker, et al., *Retrospective Analysis of Mortalities Associated with Medication Errors*, 58 AMERICAN JOURNAL OF HEALTH-SYSTEM PHARMACY 1835-1841 (2001).

<sup>39</sup> Carol Holquist & Jerry Phillips, *Curbing med errors involving Anzemet, Bentyl*, 145 Drug Topics 42 (2001), available at [www.fda.gov/cder/drug/MedErrors/anzemet.pdf](http://www.fda.gov/cder/drug/MedErrors/anzemet.pdf).

<sup>40</sup> 2003 Proposed Rule, *op. cit.*, at 12420.

<sup>41</sup> 2003 Proposed Rule, *Id.*, at 12420.

<sup>42</sup> 2003 Proposed Rule, *Id.*, at 12420.

serious, expected SADR are to be submitted – this is opposed to current regulations, which do not require submission of foreign AE reports on a periodic basis (the only mandated foreign reports, those involving serious, unexpected cases, are submitted on an expedited basis).

*Contractors:* Under proposed 314.80(a), contractor “means any person (e.g., manufacturer, packer or distributor whether its name appears on the label of the product; licensee; contract research organization) that has entered into a contract with the manufacturer to manufacture, pack, sell, distribute or develop the drug or to maintain, create or submit records regarding SADR or medication errors.”<sup>43</sup>

So defined under the Proposed Rule, contractors must submit all safety reports of SADR and medication errors to the applicant within five calendar days of initial receipt. In that regard, contracts between contractor and applicant must detail contractor responsibilities for postmarketing safety reporting.

Regrettably, the Proposed Rule does not specify whether Day 0 is the date that the contractor receives information constituting an SADR or medication error report, or the date the applicant receives the information from the contractor—the 2001 draft guidance is also silent in this regard.

This is not the case with Volume 9A, which clearly states that “[t]he clock for expedited reporting starts (day 0) as soon as the minimum information ... has been brought to the attention of any personnel of the Marketing Authorisation Holder or an organisation having a contractual arrangement with the Marketing Authorisation Holder, including medical representatives.”<sup>44</sup>

While FDA has not defined Day 0 in the case of a contractor, in 2005 it issued a finding in a warning letter stating that for reporting purposes, the company “should use the date that their business affiliate received the initial report as the time the 15-day reporting clock begins.”<sup>45</sup> This timeframe and direction is consistent with that contained in Volume 9A.

*Licensed physician(s):* The Proposed Rule states that licensed physician(s) at the company must be responsible for “content and medical interpretation” of data/information submitted in postmarketing reports (including PSURs). FDA’s stated rationale is that “[t]he medical significance of postmarketing safety reports warrants review by a licensed physician. The agency believes that licensed physicians would ensure submission of high quality reports to FDA that articulately conveys all clinically relevant information associated with an SADR.”<sup>46</sup>

### E. *Whither the Proposed Rule? Implications and Concerns*

As of this writing, the status of the Proposed Rule is unclear. FDA has made no recent announcements, and the list of guidances CDER plans to develop during 2007 includes three that are specific to drug safety information (*Contents of a Complete Submission Package for a Proposed Proprietary Drug or Biologic Name; Dear Healthcare Professional Letters; Minimum Data Elements to be Included in a Serious Adverse Event Report for Monograph OTC Products*)<sup>47</sup> that do not indicate any action will be taken regarding the Proposed Rule this year.

<sup>43</sup> 2003 Proposed Rule, *op. cit.*, at 12477.

<sup>44</sup> Volume 9A, *op. cit.*, at 55.

<sup>45</sup> [www.fda.gov/foi/warning\\_letters/archive/g5198d.pdf](http://www.fda.gov/foi/warning_letters/archive/g5198d.pdf).

<sup>46</sup> 2003 Proposed Rule, *op. cit.*, at 12413.

<sup>47</sup> FDA, Guidance Agenda: Guidances CDER is Planning to Develop during Calendar Year 2007, available at [www.fda.gov/cder/guidance/CY07.pdf](http://www.fda.gov/cder/guidance/CY07.pdf).

Criticism from PhRMA and other quarters notwithstanding, the Proposed Rule represents FDA's current thinking in 2003 as to how premarketing clinical safety and postmarketing pharmacovigilance should be performed, is based on applicable ICH, CIOMS and FDA's own safety and risk management initiatives, and culminates many years of work by agency personnel. The ramifications of continuing to follow older regulations and their associated guidances (draft and final) that, unlike the Proposed Rule, do not fully reflect current pre- and postmarketing safety performance standards are varied and concerning.

With so many pharmaceutical companies multinational entities, major safety-related regulatory documents like the European Clinical Trial Directive and Volume 9A have established standards for performing premarketing clinical safety or postmarketing pharmacovigilance that must be matched in regions technically not subject to their legal requirements. Regarding regulatory authority inspections, such documents are used as their legal basis and performed against their standards—with confidentiality arrangements [e.g., between FDA, EC and the EU's European Medicines Agency (EMA)] that enable sharing of inspectional findings and sanction inspections by foreign competent authorities, standards other (and more stringent) than those of one's own national medical product agency may well need to be followed.

Beyond these considerations, the situation for industry safety specialists in the United States is further problematic. Should they need increased personnel and funding to perform state-of-the-art premarketing and postmarketing safety and risk management activities (including many incorporated into the Proposed Rule), they are unable to cite a finalized rule for support and justification to senior non-safety management.

This is in stark contrast to Europe, where in Volume 9A the EMA has issued a comprehensive, up to date postmarketing pharmacovigilance regulatory guideline (carrying the force of law) to which safety personnel can point in similar circumstances. In addition, the Qualified Person Responsible for Pharmacovigilance (QPPV) in Europe, whose responsibilities include establishing and maintaining/managing the MAH's pharmacovigilance system, is under strict legal obligations entailing personal financial and criminal liability. In this position, which has no analogy under current U.S. law or regulation, the QPPV serves as an advocate for the provision of adequate resources for pharmacovigilance activities in Europe.<sup>48</sup>

It is further worth noting that the entire process of proposal, review, comment and release of the final Volume 9A, which applies to 27 EU Member States and three European Economic Area countries, took less than two years from start to finish.

What about FDA? Given its professionals' commitment to public health and desire to provide industry with useful information and mandates to foster compliance, reasons for the lag in regulatory activities must be found elsewhere. Inadequate resources and other priorities (such as PDUFA-mandated drug review activities) are the most likely factors, along with relatively little public concern compared to other issues.

The GAO, in its September 2002 report, "Effect of User Fees on Drug Approval Times, Withdrawals, and Other Agency Activities," concluded that "PDUFA has been successful in providing FDA with the funding necessary to hire additional

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<sup>48</sup> Elliot G. Brown, *The Qualified Person for Pharmacovigilance for Europe: A Compliance and Quality Perspective*, 19 *INTERNATIONAL JOURNAL OF PHARMACEUTICAL MEDICINE* 7-14 (2005).

drug reviewers, thereby making new drugs available in the United States more quickly.”<sup>49</sup> However, the GAO also reported that “[w]hile PDUFA has increased the funds available for FDA’s drug and biologic review activities, funds for FDA’s other activities have constituted a smaller portion of FDA’s total budget since implementation of PDUFA.”

Compliance issues (other than satisfying Phase IV commitments) have been conspicuously absent in the Congressional inquiries into drug safety, and neither of the 2006 studies by the GAO (*Improvement Needed in FDA’s Postmarket Decisionmaking and Oversight Process*)<sup>50</sup> and IOM (*The Future of Drug Safety: Promoting and Protecting the Health of the Public*)<sup>51</sup> addressed the situation or issues concerning current pharmaceutical regulations and guidances that have been presented here. Despite their importance to medical product safety, discussion of premarketing clinical safety and postmarketing pharmacovigilance inspections and related activities has been essentially non-existent in the multiple examinations of the U.S. drug safety system, and the FDA’s requested funding for drug safety-related enhancements under PDUFA IV, while certainly welcome, does not include any designated funds for inspections or other compliance functions.<sup>52</sup>

For reasons already discussed, and further inspection-related aspects to be examined later, the Proposed Rule’s ongoing indeterminate status is causing major difficulties for the pharmaceutical industry, and by extension for public health. Safety professionals who agree with many of the principles incorporated into the Proposed Rule (e.g., active query being performed by healthcare professionals and expanded expedited reporting — new information beyond individual case reports if it impacts the pharmaceutical’s benefit-risk profile; medication errors without associated serious AEs, including potential errors) and accordingly revised company processes and procedures face the real possibility that the finalized rule may differ significantly from the proposed version.

#### IV. POSTMARKET PHARMACOVIGILANCE, RISK MANAGEMENT AND CURRENT GUIDANCES

In June 2002, under signed PDUFA III legislation, FDA agreed to specific performance goals that included drafting an industry guidance on risk management activities in exchange for receipt of user fees. At the time, FDA planned to finalize three guidance documents for industry by September 30, 2004. Towards that end, in 2003 FDA drafted and released for comment three concept papers that outlined the agency’s preliminary thinking on “Premarketing Risk Assessment,” “Risk Management Programs” and “Risk Assessment of Observational Data: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment.”<sup>53</sup>

A public workshop was held in April 2003 to present FDA’s thoughts and solicit input from stakeholder groups, and in May 2004 three draft guidances for industry were released for comment:

<sup>49</sup> GAO, Effect of User Fees on Drug Approval Times, Withdrawals, and Other Agency Activities [GAO-02-958] (Sept. 2002).

<sup>50</sup> GAO, Improvement Needed in FDA’s Postmarket Decision-Making and Oversight Process [GAO-06-402] (Mar. 2006).

<sup>51</sup> IOM, *The Future of Drug Safety: Promoting and Protecting the Health of the Public* (Sept. 2006).

<sup>52</sup> HHS, FDA, Prescription Drug User Fee Act; Public Meeting [Docket No. 2007N-0005], 72 *Federal Register* 1743-1753 (2007), available at [www.fda.gov/OHRMS/DOCKETS/98fr/07-122.pdf](http://www.fda.gov/OHRMS/DOCKETS/98fr/07-122.pdf).

<sup>53</sup> [www.fda.gov/cder/meeting/riskmanagement.htm](http://www.fda.gov/cder/meeting/riskmanagement.htm).

- “Premarketing Risk Assessment;”
- “Development and Use of Risk Minimization Action Plans [RiskMAPs];”
- “Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment;”<sup>54</sup>

In March 2005, the final risk minimization guidances were issued.<sup>55</sup>

There is little doubt that the procedures FDA followed for drafting and soliciting public review and comment on the guidances were quite successful, leading to final documents of high quality and great utility, both in the United States and abroad. However, they are guidances, and neither they nor the ICH’s E2E “Pharmacovigilance Planning”<sup>56</sup> (issued as a finalized U.S. guidance in 2005) have been incorporated into FDA rules or regulations.

That is not the case in Europe, where the EMEA Committee for Medicinal Products for Human Use’s “Guideline on Risk Management Systems for Medicinal Products for Human Use”<sup>57</sup> went into effect in November 2005. Under this guideline, the EU Risk Management Plan (EU-RMP) incorporates E2E concepts regarding the Safety Specification and Pharmacovigilance Plan, with further utilization of E2E concepts throughout the document. Its “Annex A: Epidemiological methods for PASS” [post-authorization safety studies] is closely in line with E2E, and “Annex B: Methods for Risk Minimization” has elements in common with the FDA’s RiskMAP guidance.

An RMP is to be submitted with an application for a new marketing authorization, or an application entailing a significant change in a prior marketing authorization. While there are no corresponding FDA regulatory requirements, U.S. companies may be well served to pursue pharmacovigilance planning in both the pre-approval and early postmarketing periods as described in E2E in either circumstance, constituting a proactive approach to safety in line with the paradigm of risk management across a medical product’s entire lifecycle. It is unfortunately unclear from a regulatory standpoint as to whether such information should routinely be submitted to FDA as part of the NDA, unless specifically requested.

With respect to another critical regulatory document, it is rather startling that the ICH “E2D Postapproval Safety Data Management: Definitions and Standards for Expedited Reporting”<sup>58</sup> guideline has remained a draft guidance (step 2) in the United States since September 2003. Adopted by the CHMP and Japan’s national regulatory authority in November 2003 and March 2005, respectively, E2D clearly influenced the Proposed Rule and has had a major impact on international post-marketing pharmacovigilance in general.

## V. POSTMARKETING PHARMACOVIGILANCE INSPECTIONS

As previously noted, relevant FDA inspectional programs have received scant attention from the various sectors involved in assessing the US drug safety program,

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<sup>54</sup> [www.fda.gov/cder/guidance/index.htm](http://www.fda.gov/cder/guidance/index.htm).

<sup>55</sup> [www.fda.gov/bbs/topics/news/2005/NEW01169.html](http://www.fda.gov/bbs/topics/news/2005/NEW01169.html).

<sup>56</sup> HHS, FDA, E2E Pharmacovigilance Planning (guidance) (Mar. 31, 2005), *available at* [www.fda.gov/cder/guidance/6355fn1.pdf](http://www.fda.gov/cder/guidance/6355fn1.pdf).

<sup>57</sup> EMEA, CHMP, Guideline on Risk Management Systems for Medicinal Products for Human Use (Nov. 14, 2005), *available at* [www.emea.europa.eu/pdfs/human/euleg/9626805en.pdf](http://www.emea.europa.eu/pdfs/human/euleg/9626805en.pdf).

<sup>58</sup> HHS, FDA, E2D Postapproval Safety Data Management: Definitions and Standards for Expedited Reporting (draft guidance) (Sept. 12, 2003), *available at* [www.fda.gov/cder/guidance/5827dft.pdf](http://www.fda.gov/cder/guidance/5827dft.pdf).

despite their importance. While full comparison of the relatively new European pharmacovigilance inspectorates with that of CDER is beyond this article's scope (see Brown and Goldman in that regard),<sup>59</sup> highlighting certain aspects is of importance.

Until the past few years, regulatory authority postmarketing pharmacovigilance inspections were generally not performed in Europe, as opposed to the United States. Further, CDER's website posting of its own guidance to FDA field staff in enforcement of the postmarketing adverse drug experience (ADE) reporting regulations, the September 1999 "Chapter 53—Postmarketing Surveillance and Epidemiology: Human Drugs: Enforcement of the Postmarketing Adverse Drug Experience Reporting Regulations"<sup>60</sup> was a laudable, rather unique use of transparency to assist the drug industry in its efforts with compliance.

However, an updated version of that document has not been posted, and while certainly applicable and still quite useful, it predates the Proposed Rule, E2D, E2E and FDA Risk Management guidances. While the regulations in place at the time of its release are still current and thus technically continue to form the basis for inspections and their findings, the guidance does not reflect CDER's enhanced scrutiny of such aspects as the quality and scope of written procedures,<sup>61</sup> performance of literature review and signal evaluation, nor the considerable advances made in pharmacovigilance practices since 1999.

In addition, two recently released regulatory documents (Volume 9A and the UK's Medicines and Healthcare products Regulatory Agency's "MHRA Statutory Pharmacovigilance Inspection," which includes guidance for preparing a Summary of Pharmacovigilance Systems)<sup>62</sup> 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.

Again, the question as to commitment of necessary personnel and funding must be raised with respect to FDA's pharmacovigilance inspectional activities. The CDER field inspectors are not specialized to perform postmarketing pharmacovigilance inspections only, but rather may also perform Good Manufacturing Practice (GMP), Good Laboratory Practice (GLP) and/or Good Clinical Practice (GCP) inspections [personal communication].<sup>63</sup>

While many of the inspectors both in the field and FDA home office are quite experienced, the expertise and skills involved in assessing these disparate systems are such that almost no pharmaceutical company Quality Assurance personnel perform compliance audits in all four realms. In fact, to do so in more than any two areas is very unusual, and external auditors generally specialize in either safety (premarketing clinical trial and postmarketing pharmacovigilance), GCP, GMP or GLP. Asking individual FDA inspectors to perform field assessments in most or

<sup>59</sup> Elliot G. Brown & Stephen A. Goldman, *Preparing for Regulatory Inspection of Company Pharmacovigilance Systems and Practices in the European Union and United States*, in Carson PA, Dent NJ (editors), *Good Clinical, Laboratory and Manufacturing Practices: Techniques for the QA Professional*, ROYAL SOCIETY OF CHEMISTRY 57-71, Cambridge, U.K. (2007).

<sup>60</sup> FDA, CDER, Chapter 53—Postmarketing Surveillance and Epidemiology: Human Drugs: Enforcement of the Postmarketing Adverse Drug Experience Reporting Regulations (Sept. 30, 1999), available at [www.fda.gov/cder/aers/chapter53.htm](http://www.fda.gov/cder/aers/chapter53.htm).

<sup>61</sup> Stephen A. Goldman, *DRUG INFORMATION JOURNAL* (2006), *op. cit.*

<sup>62</sup> Medicines and Healthcare products Regulatory Agency, *MHRA Statutory Pharmacovigilance Inspection* (Apr. 2007), available at [www.mhra.gov.uk/home/idcplg?IdcService=GET\\_FILE&dID=33459&noSaveAs=1&Rendition=WEB](http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dID=33459&noSaveAs=1&Rendition=WEB)

<sup>63</sup> Personal communication: Carol Krueger, R.N., Consumer Safety Officer, Division of Compliance Risk Management and Surveillance, Office of Compliance, CDER, FDA (May 31, 2007).

all of these domains is antithetical to their gaining deep understanding in any one area, or realistically being able to keep current on advances specific to that field.

The situation at the MHRA medicines Inspectorate is quite different [personal communication].<sup>64</sup> Nearly all their inspectors have several years experience in their specialist field before joining the Inspectorate, as they do not employ new graduates as inspectors. Their professional backgrounds are diverse, including physicians, pharmacists, chemists, information technology specialists and biologists.

MHRA's medicines Inspectorate uses specialist inspectors in five areas: GCP, Good Distribution Practice (GDP), GLP, GMP and pharmacovigilance—although most specialize and work in one particular area, a small percentage are cross-trained to inspect in more than one. The MHRA Inspectorate encourages cross-training, but the inspectors retain one core specialty and spend most of their time working in that discipline.

## VI. CONCLUSION

In the United States, ongoing analysis of the national program for drug safety has already led to changes, both implemented and recommended, that are intended to enhance FDA's ability to protect public health via increased funding for new personnel, upgraded methods and available data, along with organizational and structural changes at the agency. It is conceivable that FDA may be granted authority to mandate both labeling changes and studies designed to monitor known and discover unknown safety concerns in the postmarketing realm.

Any constructive actions that increase the likelihood of safe use of effective pharmaceuticals in the United States are most welcome, and open, frank dialogue across all involved sectors in service of public health is to be applauded.

However, the numerous investigations of FDA's postmarketing drug safety program, scientific literature and associated media coverage have almost completely ignored both the critical role of FDA's inspectional programs for pharmaceutical adverse event reporting compliance, and the significant impact of delays in finalization and release of needed rules, regulations and guidances related to drug safety.

For assessment of this country's pharmaceutical safety program to be comprehensive, and appropriate steps taken, attention must be paid to these vital aspects. For this to take place, premarketing clinical safety and postmarketing pharmacovigilance specialists need to be given opportunities to express their views and concerns in open forums, informal and official, and advocate for needed funding and personnel for crucial pharmaceutical safety-related compliance and regulatory activities at FDA.

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<sup>64</sup> Personal communication: Anya Sookoo, Ph.D., Medicines and Healthcare products Regulatory Agency, Expert Inspector, GCP & Pharmacovigilance (June 1, 2007).