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Spontaneous Reporting Systems: Achieving Less Spontaneity and More Reporting

by Jessamyn S. Berniker

Introduction

Spontaneous reporting systems are used worldwide as a means of collecting information on adverse drug reactions and events.¹ Although the systems vary, they generally solicit reports from medical health practitioners of serious or unexpected medical reactions that may have been caused by a medication. The compilation of reports allows organizations like the Food and Drug Administration to see common reactions or unusual patterns of activity around certain medications, thereby indicating that heightened precaution or further study may be desirable. Despite thorough pre-market testing, spontaneous reporting systems are valuable because clinical trials only test small sample sizes and do not test combinations of medications or products.

Additionally, individual variability in drug metabolism can lead to very different patient responses to med-

¹The term “adverse drug reaction” has been defined differently by different sources but it generally describes a response to a medicine that is unexpected, unintended, undesired or excessive. Technically the term “adverse drug events” (“ADEs”) “encompasses both medication errors and ‘adverse drug reactions.’” (“ADRs”) Jerry Phillips, RPh, *FDA Efforts at Minimizing the Risks of Preventable Adverse Drug Events*, <http://www.medscape.com/medscape/pharmacists/journal/2000/v01.n04/mph7174.phil/mph7174.phil-01.html> (posted July 1, 2000) (last accessed April 6, 2001). The literature about spontaneous reporting often seems to omit express acknowledgement of this distinction. The Food and Drug Administration in the United States requests reports of adverse drug events, while most other spontaneous reporting systems worldwide request reports of adverse drug reactions. For the purpose of this article, the term “adverse drug event” will be used whenever a reference denoted data as adverse drug event information, in the description of U.S. policy, and in discussions relating to both medication errors and adverse drug reactions. The term “adverse drug reaction” will be used in the description of all other foreign data and discussions unrelated to medication errors.

ications. Therefore, continued monitoring of these products is necessary to ensure public safety.^{2,3} There is little doubt that doctors and other health care professionals are uniquely situated to receive and report this information.⁴ Although countries around the world rely on spontaneous reporting systems as safety indicators, reporting rates by health care professionals are dismal, usually in single digit percentages.

The purpose of this article is to highlight and analyze possible improvements to spontaneous reporting systems, in particular, and drug safety, in general. Part I of this article will provide a background on adverse drug reactions and spontaneous reporting systems, with particular emphasis on the MedWatch reporting system currently used in the United States. Part II will discuss physician attitudinal studies performed worldwide that have attempted to highlight the reasons for the underreporting of adverse reactions and problems with reporting systems. Part III will analyze problems identified with spontaneous reporting systems and potential improvements of them.

²See also Laurence Landow, M.D., *Monitoring Adverse Drug Events: The Food and Drug Administration MedWatch Reporting System*, 23 REG'L ANESTHESIA & PAIN MED. 190, 191 (1998) (51% of approved drugs are associated with adverse effects not detected before approval).

³It is important to note that FDA "does not require that postmarketing studies routinely be performed to determine the rates of ADEs." Rebecca S. Gruchalla, M.D., Ph.D., *A One-year Perspective on MedWatch: The Food and Drug Administration's new medical products reporting program*, 95 J. ALLERGY & CLINICAL IMMUNOLOGY 1153, 1153 (1995).

⁴See Peter H. Rheinstein, MD, MS, *MedWatch: The FDA Medical Products Reporting Program*, 48 AM. FAM. PHYSICIAN 636, 638 (1993); cf. David A. Kessler, MD *Introducing MedWatch A New Approach to Reporting Medication and Device Adverse Events and Product Problems*, 269 JAMA 2765, 2765 (1993); see also Mary Pat Couig & Ruth B. Merkatz, *MedWatch: the New Medical Products Reporting Program*, 93 AM. J. NURSING 65, 66 ("Because nurses are the largest group of health professionals and have more constant, direct contact with patients in the hospital, home, and in ambulatory care settings than any other group, nurses are in a unique position to identify and report adverse effects of drugs, biologics, medical devices, and special nutritional products such as medical foods.").

I.

Background on Adverse Drug Reactions and Reporting

The incidence of adverse drug events and reactions is amazing. Adverse drug events are estimated to account for about 106,000 deaths in the United States each year, more than auto accidents, suicides, and homicides combined,⁵ making adverse effects of drugs one of the top six causes of death in this country.⁶ One study found that between 3 and 11% of hospital admissions could be attributed to adverse drug reactions.⁷ Other studies have reported that between 10 and 20% of all hospitalized patients will experience adverse drug events while in the hospital.⁸ Drug-related morbidity and mortality costs in the billions of dollars annually in the United States.⁹

This section will first discuss the causes of adverse drug events and mechanisms for reducing their frequency. It will then provide a general background on reporting systems and specific details about the Food and Drug Administration's MedWatch system.

⁵See Landow, *supra* note 2, at 190.

⁶See Alastair J.J. Wood, MD et al., *Making Medicines Safer – The need for an Independent Drug Safety Board*, 339 NEW ENG. J. MED. 1851, 1852 (1998).

⁷See Kessler, *supra* note 4, at 2765.

⁸See *Protecting the Identities of Reporters of Adverse Events and Patients; Preemption of Disclosure Rules*, 59 Fed. Reg. 3944, 3945 (1994).

⁹See Charles Marwick, *MedGuide: At Last a Long-Sought Opportunity for Patient Education about Prescription Drugs*, 277 JAMA 949, 949 (1997); *see also*, Michael A. Friedman, MD et al., *The Safety of Newly Approved Medicines: Do Recent Market Removals Mean There is a Problem?*, 281 JAMA 1728, 1732 (1999) (“Expected toxic effects from marketed drugs, even when used appropriately, is estimated to rank among the top 10 causes of death in the United States and is estimated to cost more than \$30 billion annually.”).

A.

What causes adverse drug events?

Allergic reactions and combinations of incompatible medications often cause adverse drug events. These occur because of our inability to know everything about a drug and its potential effects before it is marketed. However, some adverse drug events are caused, or at least perpetuated, by human practices. These include patient non-compliance with medication recommendations, mistakes and administrative errors. With increased attention, both of these types of drug events could be minimized.

Adverse reactions are commonly caused by allergic reactions to medications and interactions between multiple medications. Any given medication will cause allergies in some proportion of patients, and often the allergies will not be foreseeable prior to use of the drug. Interactions between multiple medications are often not determined in the pre-market phase of drug testing, so they too can cause ADRs in patients taking more than one drug. Although these complications seem unpreventable, there are ways to minimize their occurrence. Focusing attention and study on particular groups who suffer more frequently from drug allergies and medication interactions could reduce their prevalence.

Gender and age differences create distinct adverse events and complicate a doctor's ability to diagnose problems. A 1994 article in the JOURNAL OF ADOLESCENT HEALTH stressed the importance of focusing on adverse events occurring in adolescents.¹⁰ The FDA has no policy encouraging testing on adolescents as it does on pediatric, geriatric and gender groups, thus post-marketing studies are particularly important for

¹⁰Stuart L. Nightingale, M.D. & Freddie Ann Hoffman, M.D., *MedWatch and Adolescence*, J. ADOLESCENT HEALTH 279 (1994).

the adolescent group.¹¹ Adolescents have reactions that are particularly hard to predict because

metabolic and hormonal alterations may confound the effects of drugs and other products used during this time period. Because the changes do not occur all at once and may vary from individual to individual the special needs of adolescents may be difficult to ascertain as a population, and the adverse effects of drug and device products can easily go unrecognized.¹²

Even when used correctly, there exists the potential for interaction between, for example, medications and the teenager's changing hormonal balance.¹³ However, monitoring teenagers to learn about their adverse events is quite difficult since they seek autonomy and independence in taking medications.¹⁴ One further difficulty, as the article suggested, is that teens are also likely to misuse medications and not follow labels causing a different set of ADEs.¹⁵ Among other things, this means that before doctors or pharmacists report adverse events from teenagers, they should verify that their patient used the medication correctly. Overall, awareness of and attention to the increased medication risks for adolescents could be helpful in dealing with these problems.

Other groups also face an increased risk of adverse drug events. Wrong doses often create adverse reactions in children.¹⁶ Surprisingly, it is not clear whether the elderly are particularly at risk. An article in the ARCHIVES OF INTERNAL MEDICINE in 1991 discussing adverse drug reactions concluded that when analyzed per drug exposure, reaction rates for the elderly were not higher than for younger groups.¹⁷ Nevertheless, the United Kingdom's Committee on Safety of Medicines ("CSM") has included adverse reactions in children and the elderly among their "areas of particular interest" for monitoring.¹⁸ The same 1991 study found that across

¹¹ See *id.* at 279.

¹³ See *id.* at 280.

¹⁴ See *id.*

¹⁵ *Id.* at 280.

¹⁶ See *Institute of Medicine Report: To Err is Human: Building a Safer Health System*, Washington, DC: National Academy Press, p.28, November 29, 1999, available at http://bob.nap.edu/html/to_err_is_human/. (last accessed April 9, 2001).

¹⁷ Gerald A. Faich, MD, MPH, *National Adverse Drug Reaction Reporting*, 151 ARCHIVES INTERNAL MED. 1645, 1646 (1991).

¹⁸ Committee on Safety of Medicines web page, accessible through <http://www.open.gov.uk> (last accessed April 6, 2001). The other "particular interests" are delayed drug effects (long term effects), congenital anomalies (they might be adverse reactions

all age groups about 60% of adverse drug reaction reports involved females.¹⁹ In general, it seems that certain gender and age qualities may be risk factors for medication problems.

It is clear that under-informed patients cause a large portion of adverse drug events.²⁰ Patient compliance with medication is difficult to determine.²¹ It is estimated that between 30-55% of patients do not follow prescribed drug regimens, largely due to lack of information,²² and some have estimated that compliance with long-term self-administered medication treatments is only about 50 percent.²³ Initially, this creates difficulties for physicians who try to distinguish between non-compliance and lack of therapeutic efficacy. In addition, failures to follow prescribed regimens result in therapeutic failures and adverse drug events. For example, skipping doses and then trying to make them up by taking multiple doses over a condensed period of time can result in ADEs. Also, failing to take a drug according to instruction could result in it being ineffectual and a new drug being prescribed, causing an unnecessary increase in adverse event risk. Since drug-related morbidity and mortality costs are in the billions, plans for getting more information to patients have been mandated. However, there is no way to monitor these efforts to see if they are effective and no way to enforce them. Currently, patients receive information largely in the form of printouts given with prescription medications. While this creates more patient awareness, some members of the medical community believe that these pamphlets place too much emphasis on the dangers of medications and not enough information on their benefits. Doctors are also concerned about pharmacists playing too big a role

to some medication used prior to birth) and herbal remedies (they may cause ADRs). *Id.*

¹⁹Faich, 151 ARCHIVES INTERNAL MED. at 1645-46, *supra* note 17.

²⁰See Marwick, *supra* note 9, at 949.

²¹See Barbara J. Stephenson, RN et al., *Is the Patient Taking the Treatment as Prescribed?*, 269 JAMA 2779, 2780 (1993).

²²See Justina A. Molzon, *The FDA's Perspective on the Future of Pharmacy*, Address at the Drake University Law School and College of Pharmacy Symposium on The Evolving Pharmacy Jurisprudence (April 9, 1994), *in*, 44 DRAKE L. REV. 463, 465-66 (1996).

²³See Stephenson et al., *supra* note 21, at 2779.

in providing medical information, especially verbally.²⁴ The FDA itself has emphasized the importance of informing patients and eliminating the gap between “what patients need to know about their drugs, and what they actually learn about them from their physician and pharmacist.”²⁵

Other studies have shown that many adverse drug events are caused by administrative errors or mistakes and therefore can be prevented. The magnitude of these errors was discussed by the Institute of Medicine, which published a lengthy report on the subject in 1999, including recommendations on how to improve patient safety overall and reduce medical errors.²⁶ In an effort to reduce mistakes of this kind, a study in the JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION tested the efficacy of a computer alert system in identifying potential ADEs.²⁷ It stated that 28-56% of ADEs are preventable, and that these are mostly caused by errors in order writing, present in up to 5% of all prescriptions.²⁸ Other times wrong doses or wrong medications are prescribed, due to lack of information about the drug or patient.²⁹ Computer systems can reduce errors by efficiently cross-checking new medications with existing patient records. The computer system used in the study reduced adverse drug event injuries at a rate of 64 per 1000 patient admissions in this way.³⁰ It is clear that the implementation of a computerized system and other error prevention mechanisms should be seriously considered by health organizations.

²⁴ See Marwick, *supra* note 9, at 949.

²⁵ Molzon, *supra* note 22, at 466.

²⁶ *Institute of Medicine Report*, *supra* note 16.

²⁷ Robert A. Rasche, MD, MS et al, *A Computer Alert System to Prevent Injury from Adverse Drug Events*, 280 JAMA 1317 (1998).

²⁸ *Id.* at 1317.

²⁹ See *id.*

³⁰ *Id.* at 1317, 1319.

B.

Background on reporting systems

1.

Generally

Spontaneous reporting systems worldwide have similar processes for acquiring and handling ADR information. A local or national agency is responsible for accumulating ADR data from medical professionals. When medical professionals encounter ADRs they are either required or requested to fill out a form describing the event and the conditions leading up to it. This can usually be sent directly to the agency responsible or to the drug manufacturer. Often the drug companies are required to forward copies of their forms to the central agency. The agency compiles the information, looking for suspicious trends that may represent drug reactions. At that point the agency can take preventative measure such as adding warnings to the product labeling or in the extreme case, recalling the product. Therefore, increasing the frequency of ADR reporting will often accelerate the agency's ability to notice reaction patterns and will allow it to take preventative measures more quickly.

Reporting rates of spontaneous reporting systems worldwide, both voluntary and mandatory, are extremely low. Even in the United Kingdom, the leader in this field, only about 10% of adverse drug events are reported.³¹ It is estimated that in the United States in the mid-1980's only 1% of adverse drug events were reported, with the number rising to 5.2% in 1994 following changes to the reporting system.³²

³¹See Landow, *supra* note 2, at 192.

³²See *id.* See generally Stephen A. Goldman, MD, Dianne L. Kennedy, RPh, MPH, *MedWatch: FDA's Medical products reporting program*, 103 POSTGRADUATE MED. 13, 13 (1998) (discussing a study where not one of the physicians contacted had ever reported an ADR despite having clinically observed serious ADRs).

It is noteworthy that until they take preventative measures, agencies and companies do not usually provide access to their information and data, to the chagrin of some physicians who desire immediate access.³³ A 1994 letter in the JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION (“JAMA”) questioned the FDA’s practice of not providing medical professionals with access to the data.³⁴ The doctors who wrote in explained that while physicians are expected to report information, they are not given access to the data unless they pay hundreds of dollars for printouts on a single drug.³⁵ A response by FDA doctor Stuart Nightingale explained that the FDA does not provide information about problems with medications or products until causality has been established, at which point Dear Health Professional Letters and the FDA Medical Bulletin are means of distributing updates.³⁶

Dr. Nightingale identified some of the problems with an open access system. To begin with, in any given ADE case associations between the medication and the adverse event may or may not be established. Furthermore, it is unclear how many unreported instances of adverse events occur and how many people are taking the medication, so one cannot assess the frequency of ADEs. Another response to the JAMA letter, by Dr. John D. Siegfried, explained that drug event reports are often incomplete, do not provide follow up information, and are usually further complicated by the parallel use of other medications and the effects of other diseases.³⁷ He emphasized that the database is not intended as a case management tool and cannot be

³³See Cheryl L. Vogt, PharmD & Patricia J. Byrns, MD, *Adverse Drug Reactions: Getting Information Back from MedWatch*, 272 JAMA 590, 590 (1994); W.H.W. Inman, *Attitudes to Adverse Drug Reaction Reporting*, 41 BRIT. J. CLINICAL PHARMACOLOGY, 434, 434 (1996) (regarding similar complaints about the British spontaneous reporting system).

³⁴Vogt & Byrns, *supra* note 33, at 590.

³⁵*Id.*

³⁶Stuart L. Nightingale, MD, *In reply: Adverse Drug Reactions: Getting Information Back from MedWatch*, 272 JAMA 590, 591 (1994).

³⁷John D. Siegfried, MD, *In reply: Adverse Drug Reactions: Getting Information Back from MedWatch*, 272 JAMA 590, 591 (1994).

used for that purpose.³⁸ The data would not be useful from an epidemiological perspective, since reported adverse events are its only mechanisms for detecting the potential of developing a problem. These limitations on adverse event reporting data and the likelihood of misuse of that data may explain why the FDA, as well as pharmaceutical companies, generally refrain from distributing the data they collect.

2.

The current state of United State's system

In an attempt to improve its reporting system, the United States introduced its newly named “MedWatch”³⁹ system in June 1993 while Dr. David Kessler was Commissioner of the Food and Drug Administration. At the same time, Dr. Kessler published a letter in the JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION explaining the need for an improved post-market reporting system and highlighting the changes made to create MedWatch.⁴⁰ Dr. Kessler cited to a then-current study saying that only 1% of serious adverse events were reported to FDA.⁴¹ He contended that there were multiple reasons for underreporting by physicians. To

³⁸*Id.* Dr. Siegfried’s explanation is similar to that of Dr. Gerald Faich, the former FDA Director of Epidemiology and Biostatistics Center for Drugs and Biologics:

[O]ne or even many reports of adverse reactions often do not provide sufficient information to confirm that a drug caused the reaction. A reaction may be caused by the suspect drug, another drug that a patient is taking, or the underlying diseases for which the drug was prescribed; it may also be entirely coincidental. Thus, adversereaction monitoring should be viewed primarily as a means for identifying potential problems.

(citations omitted) Gerald A. Faich, MD, MPH, *Special Report: Adverse-Drug-Reaction Monitoring*, 314 NEW ENG. J. MED. 1589, 1591 (1986).

See also, Richard I. Shader, MD, David J. Greenblatt, MD, MEDWATCH, *the New FDA Averse Effects Reporting System*, 13 J. OF CLINICAL PSYCHOPHARMACOLOGY, 303, 303-04 (1993) (“The system is intended to provide and *initial signal* on the *possible* association of a drug (or device) with an unusual, unexpected or serious adverse event. The *signal* by itself is not conclusive and does not prove cause and effect. Any implied association must be followed by further study using appropriately rigorous experimental, clinical, or epidemiologic methods.”) (emphasis in original).

³⁹Although this name was first used in 1993, the United States had a spontaneous reporting system prior to MedWatch.

⁴⁰Kessler, *supra* note 4.

⁴¹*Id.* at 2765 (citing H.D. Scott, S.E. Rosenbaum et al., *Rhode Island physicians’ recognition and reporting of adverse drug*

begin with, doctors may not link the unexpected outcome of treatment with the drug or device but instead think the reaction is related to the disease itself. He conceded that this is largely due to limited medical training in pharmacology and therapeutics.⁴² Second, notification of these problems to the FDA was not yet ingrained in medical professionals in the United States, as it was in the United Kingdom.⁴³ Third, too much paperwork was making reporting tedious. Finally, he asserted that doctors were unclear on what should and should not be reported.⁴⁴

The MedWatch system was set up to alleviate these problems. MedWatch functions on mandatory reporting from manufacturers and voluntary reporting from physicians.⁴⁵ The reporting process has been reduced to a one-page form that is identical for each type of FDA-regulated product (except vaccines which are treated separately). Physicians have the option of reporting directly to the FDA or to drug manufacturers, who are required to forward the reports to the FDA. In 1996, 9.0% of the reports were submitted directly to FDA, while manufacturers submitted 91% of the reports to FDA. Reports sent in by the manufacturers that described events not included in the official FDA literature for medications, known as 15-day reports, accounted for 15.6% of the total.⁴⁶ In his letter, Dr. Kessler expressly noted that physicians should not

reactions, 70 R.I. MED. J. 311 (1987)); see also David W. Bates, MD, MSc. et al., *Relationship between Medication Errors and Adverse Drug Events*, 10 J GEN INTERNAL MED 199, 199 (1995) (“[S]pontaneous reporting, the usual means of ADE identification, overlooks as many as 95-99% of ADE’s that are detectable by other methods.”).

⁴²Kessler, *supra* note 4, at 2765. See generally David W. Nierenberg, MD, *Clinical Pharmacology Instruction for all Medical Students*, 40 CLINICAL PHARMACOLOGY & THERAPEUTICS 483 (1986) (discussing the need for more emphasis on clinical pharmacology in medical school).

⁴³Kessler, *supra* note 4, at 2765.

⁴⁴*Id.* at 2765, 2767.

⁴⁵“Reporting of postmarket ADEs by health professionals and consumers is voluntary. They may send their reports directly to FDA, to the manufacturer or both. Drug manufacturers are required by law and regulation to submit to FDA postmarket ADR reports received by any means from health professional or consumers.” <http://www.fda.gov/cder/dpe/annrep96/index.htm> (last accessed April 6, 2001).

“There are three types of reports in the FDA computerized postmarket ADE database: 1. Manufacturer-reported cases concerning ADEs not in present official FDA labeling with serious outcomes (i.e., death, life-threatening, hospitalization, permanent disability, congenital anomaly, cancer, or overdose). These cases are known in regulatory language as “15-day Alert Reports” because the manufacturer has 15 working days to submit this type of report to FDA. 2. All other manufacturer-reported cases. These cases are known in regulatory languages as “Periodic Reports” because the manufacturer is required to submit them to FDA on a cyclical basis. 3. Cases sent directly to FDA by health professionals or consumers (“Direct Reports”).
Id.

⁴⁶<http://www.fda.gov/cder/dpe/annrep96/index.htm> (last accessed April 6, 2001).

report every adverse event observed due to the impracticality for the doctors and the FDA. Instead, only *serious events* should be reported: those related to death, a life threatening condition, initial or prolonged hospitalization, disability, congenital anomaly, or when intervention is required to prevent permanent impairment or damage.⁴⁷ In addition, Dr. Kessler explained that doctors should report a problem even if they are only *suspicious* of a link between a regulated product and a serious event. He emphasized that there need not be a definite connection, and that they do not have to wait for compelling evidence. Upon encountering a suspicious data set, the FDA's options include: issuing warnings, making labeling changes, requiring manufacturers to conduct post-marketing studies, and ordering product withdrawals. In 1993, the FDA launched a large-scale advertising effort to inform physicians of MedWatch, its procedures and the benefits of reporting.

MedWatch does not verify or validate reaction reports to determine whether or not they actually occurred or could plausibly have been caused by the drug or device.⁴⁸ This would require significant resource expenditure. There has not been much discussion in the literature of inaccurate reports, although one can imagine a situation where someone who has a grudge against a certain company would attempt to sabotage their product.

⁴⁷Kessler, *supra* note 4, at 2768.

Later articles, authored in part by MedWatch director Dianne Kennedy, restrict reporting to events that are serious and *unexpected*, unexpected meaning not currently in the official labeling for the drug. See Goldman, *supra* note 32, at 14; Toni D. Piazza-Hepp & Dianne L. Kennedy, *Reporting of Adverse Events to MedWatch*, 52 AM. J. HEALTH-SYS. PHARMACY 1436, 1439 ("Reporting well-known adverse reactions to older drugs to FDA is generally not encouraged unless there is suspicion of a generic drug product inequivalency, other product problem, previously unknown drug interaction, or some other unusual circumstance. MedWatch data are not used to calculate the frequency of particular adverse events in clinical practice but rather to signal safety concerns and generate appropriate responses.").

⁴⁸See Shader, *supra* note 38, at 304.

II.

Attitudinal Studies on Underreporting by Physicians

Several attitudinal studies from around the world are presented in Table 1, Appendix A for use in this discussion. The compilation highlights issues central to medical practitioners when deciding whether to report adverse reactions. Since the studies in Table 1 will be used demonstratively throughout the article, this section will briefly summarize each study and will conclude with a discussion of their limitations.

A.

Compilation of attitudinal studies

1.

Background on the European Union study⁴⁹

A study conducted in 1993-94 attempted to compare doctors' attitudes to adverse reaction reporting systems in European Union countries.⁵⁰ The same questionnaire, with a few variations for individual countries,⁵¹ was sent to doctors in Denmark, France, Ireland, Italy, the Netherlands, Portugal, Spain, Sweden, and the United Kingdom.⁵² The authors indicated that over-interpretation of the results would not be advisable due

⁴⁹K. J. Belton & The European Pharmacovigilance Research Group, Attitude Survey of Adverse Drug-Reaction Reporting by Health Care Professionals Across the European Union, 52 Eur. J. Clinical Pharmacology 423 (1997).

⁵⁰*Id.* at 424.

⁵¹*Id.* at 425.

⁵²*Id.* at 423.

to potentially disproportionate sample sizes and over-representation of some types of medical professionals in parts of the studies.⁵³ It is noteworthy that while Portugal actually requests that all ADRs be reported, Ireland, Holland, Spain and the United Kingdom request reports only for serious reactions and reactions to new drugs.⁵⁴

2.

Background on the Northern Italian study⁵⁵

In 1997 a study was published in PHARMACOLOGICAL RESEARCH detailing attitudes toward adverse drug reaction reporting by medical practitioners in a district in northern Italy.⁵⁶ This study attempted to determine why doctors were underreporting reactions. In Italy, a structured national reporting scheme has not yet been fully established. Italian law requires doctors to notify the Area Health Authorities of suspected ADRs, and those agencies are required to send the reports to the Ministry of Health. Imbalances between districts in the Italian system suggest that it does not function efficiently. Nearly 40% of the total ADRs reported in 1994 came from regions whose populations comprised only 17% of Italy's total population. In 1994 the area studied in this article, Varese, Italy, had over 300,000 inhabitants but only 3 ADR reports, a very low number. Regardless, reporting rates for all of Italy are not particularly impressive. In 1992 only 75 reports

⁵³*Id.* at 426.

⁵⁴*Id.* at 427; Karen J. Belton et al., *Attitudinal Survey of Adverse Drug Reaction Reporting by Medical Practitioners in the United Kingdom*, 39 BR. J. CLINICAL PHARMACOLOGY 223, 225 (1995).

The UK's Committee on Safety of Medicines also specifically wants not only proven ADRs but also suspected ones. *Id.* at 226.

⁵⁵Marco Cosentino, et al., *Attitudes to Adverse Drug Reaction Reporting by Medical Practitioners in a Northern Italian District*, 35 Pharmacological Research 85 (1997).

⁵⁶*Id.* at 85.

per million inhabitants were sent from Italy to the World Health Organization Collaborating Center. As a basis for comparison, the corresponding rates for Denmark and Germany were 429 and 407, respectively.⁵⁷

3.

Background on the Irish study⁵⁸

A 1999 study of Irish doctors focused on the relationship between their attitudes and underreporting. This survey included both general practitioners and hospital doctors, but separated the data for comparison purposes. Overall, however, there was little difference between the responses of the general practitioners and the hospital-based doctors. It is worth noting that unlike the MedWatch system, the Irish Medicines Board requests reports on *all* ADRs.⁵⁹

4.

Background on the Dutch study⁶⁰

⁵⁷ *Id.*

⁵⁸ D. Williams & J. Feely, Underreporting of Adverse Drug Reactions: Attitudes of Irish Doctors, 168 *Irish J. Med. Sci.* 257 (1999).

⁵⁹ *Id.* at 259.

⁶⁰ I. A. Eland et al., Attitudinal Survey of Voluntary Reporting of Adverse Drug Reactions, 48 *Brit. J. Clinical Pharmacology* 623 (1999).

A Dutch survey published in 1999 endeavored to determine reporting attitudes by ascertaining past behavior, questioning participants about whether they would report hypothetical medical reactions, and comparing the answers of different types of doctors.⁶¹ In accordance with predicted rates of adverse reactions, 98% of the entire group of respondents had diagnosed an ADR in one of their patients.⁶² Overall those participants who had previously reported an ADR were more inclined to report the hypothetical ones.⁶³

5.

Background on the Northern Region of the United Kingdom study⁶⁴

In 1992, a British survey was published which tried to compare attitudinal differences between medical communities with high and low reporting rates.⁶⁵ As the South African study, *infra*, mentioned, 80% of the ADRs in the United Kingdom are submitted by 7.4% of its doctors.⁶⁶ The Irish article also provided some information about United Kingdom reporting rates. It is estimated that in the UK, which has utilized the “Yellow Card” system for reporting adverse drug reactions to the Committee on Safety of Medicines since 1964, only 10-15% of severe reactions are reported.⁶⁷ The CSM solicits serious suspected ADRs from established drugs and all suspected ADRs from new drugs.⁶⁸

⁶¹ *Id.* at 624.

⁶² *Id.*

⁶³ *Id.* at 625.

⁶⁴ D. N. Bateman, et al., Attitudes to Adverse drug reaction reporting in the Northern Region, 34 *Brit. J. Clinical Pharmacology* 421 (1992).

⁶⁵ *Id.* at 421.

⁶⁶ See Ashley H. Robins, M.D., D.P.M., M.R.C. PSYCH. et al., *Attitudes to Adverse Drug Reactions and their Reporting Among Medical Practitioners*, 72 *S. AFR. MED. J.* 131, 134 (1987).

⁶⁷ See Williams, *supra* note 58, at 259.

⁶⁸ See Bateman, *supra* note 64, at 425.

The study proposed various statements to the participants and had them respond in agreement or disagreement. Personal liability concerns ranged from 9-20% of those surveyed. Interestingly, between 26-30% of the general practitioners felt that they should be financially reimbursed. The corresponding numbers for consultants and junior hospital doctors were much lower, at 8-14% and 8-23% respectively. The lower figures in each set represented responses from the “high” reporting districts.⁶⁹ The data on financial reimbursement is hard to compare with other studies since none of the others directly solicited this information. Overall, the study’s authors seemed to think that education might improve reporting rates.⁷⁰ They felt that the attitudes that surfaced in the study showed that the doctors were clearly aware of the system but lacked the requisite knowledge to “contribute to it optimally.”⁷¹

6.

Background on the South African study⁷²

This study focused on private practitioners in the Cape Town region of South Africa and analyzed the reporting habits of general practitioners, medical specialists and surgical specialists.⁷³ Their reporting practices were of concern because 97% of the doctors in the Cape Town region did not report a single ADR within the course of a year.⁷⁴ The authors concluded that few doctors regarded reporting as part of handling ADRs in their practice.⁷⁵

⁶⁹ *Id.* at 426.

⁷⁰ *Id.*

⁷¹ *Id.*

⁷² Robins, *supra* note 66.

⁷³ *Id.* at 131.

⁷⁴ *Id.* at 134.

⁷⁵ *Id.* at 131, 133.

The South African study concluded that there was significant doubt as to whether further attempts to inculcate positive attitudes would substantially improve motivation to report adverse reactions.⁷⁶ The authors did not clearly explain why this was their conclusion, except to imply that mandatory reporting would not solve the problem.

B.

Limitations of these studies

Although the studies assessing the reasons for underreporting may be useful for maximizing drug reaction information, it is not clear that they accurately represent the reasons for underreporting in the United States and elsewhere. Since they were not performed in the United States, they may reflect attitudinal differences that result from variations in each country's individual spontaneous reporting system. Additionally, many health care professionals may not be aware of the extent some factors influence their decision not to report. Without a specific question to trigger the respondent's thought process, these unapparent factors may not emerge. One can speculate that the results in the studies are largely correlated to the questions asked. For example, a potentially critical background factor such as the reporting attitudes in the health professional's working environment may be unapparent to the survey respondent. Yet no study asked how many physicians knew other physicians who had ever reported ADRs. None asked how many were affirmatively encouraged by anyone in their office to report. None asked whether any patient had ever asked them to report an ADR and how it would have affected them if they had been asked. Although these questions were not asked, they represent factors that may still be quite relevant to underreporting, but for which there is little statistical

⁷⁶*Id.* at 134.

support. The essential point is that these studies should not be regarded as the final word on explanations for underreporting or possible solutions to the problem. A final limitation of the studies regards the response rates. The response rates for the surveys ranged from 19.7%⁷⁷ (the Spain portion of the EU survey) to 77%⁷⁸ (the Sweden portion of the EU survey), with second place going to the Northern United Kingdom study at 74%.⁷⁹ Less than perfect response rates often raise questions about the sample,⁸⁰ and one cannot help suspect a correlation between the likelihood of responding to a survey with the likelihood of spontaneously reporting.⁸¹

What is initially noticeable about the Italian and Dutch surveys is that their results do not seem at all similar to their respective portions of the European Union study. Oddly, although the Italian study focused on a particularly weak reporting area, its data indicated that its participants report much more often than those in the European Union-Italian study, which was nationwide. This casts significant doubt on the ability of these studies to accurately represent reporting rates. However, they may still be relatively useful for descriptive purposes, for instance in analyzing why doctors do not report. Given no reason to believe one study more accurate than another, they have all been included. Unlike the Italian and Dutch surveys, the results of the two United Kingdom-based surveys, displayed in Table 1, were somewhat similar.

For these reasons, the studies should be looked at as demonstrative aids, not as accurate reflections of physician attitudes.

⁷⁷Belton, 52 EUR. J. CLINICAL PHARMACOLOGY at 424, *supra* note 49.

⁷⁸*Id.*

⁷⁹Bateman, *supra* note 64, at 421.

⁸⁰*See* Williams, *supra* note 58, at 258.

⁸¹In a Letter to the Editor published in the BRITISH JOURNAL OF CLINICAL PHARMACOLOGY, W. H. W. Inman, developer of the United Kingdom's Yellow Card system questioned the validity of the United Kingdom portion of the European Union study published in 1995 and described above. He stated,

It seems doubtful, however, if the author's survey could give valid conclusions when only 57% of the doctors in their sample returned questionnaires, in spite of reminders to non-responders. It is very unlikely, for example, that doctors who were worried about legal liability or had feelings of guilt for having harmed a patient would have admitted this and returned the questionnaires.

Inman, *supra* note 33, at 434.

III.

Limitations of Spontaneous Reporting Systems and Improvement Options

This section will discuss problems with spontaneous reporting systems worldwide and analyzes potential avenues for handling them. The issues include: whether reporting and how to report is instilled in physicians, the quality of reports, uncertainty as to whether a drug caused a reaction, time pressures that hinder reporting, liability concerns of reporting, publishing aspirations that stifle reporting, and patient involvement in reporting.

Before proceeding, it may be worth questioning the assumption throughout this piece that it would be preferable to increase reporting rates. While 5.2% reporting may be too low, 100% reporting may be neither feasible nor ideal. The handling costs of this much reporting would be very high and it is likely that the time saved would be marginal. To find the ideal reporting rate, it would be worthwhile analyze how much data is required for the FDA to take definitive preventative action, how quickly it can be accumulated and how much healthcare time ought to be sacrificed for this cause. Assuming that the ideal rate is somewhere between the current 5.2% rate and complete reporting, it may be worthwhile to adopt some of the methods discussed below that would increase the quantity of ADE reports filed. Options for improving the quality of reporting are also described in this section.

A.

Reporting is not fully “ingrained”

One reason commonly cited for low reporting rates is that reporting is not ingrained in practitioners; it is not habitual. While this lack of routineness may affect reporting rates, it is worth noting early on that there are many other obstacles to the quantity of reports being filed. These are discussed further in the piece.

1.

Frequency of reporting

Data from around the world shows that reporting is not habitual. Despite the revamping of the spontaneous reporting system, it is not clear that American physicians are ingrained with ADE reporting habits. While the mid-1980's estimate of 1% reporting quintupled by 1994 post-MedWatch, over 94% of all reportable adverse events are still not reported in the United States.⁸² A minimum of 30% of respondents in the foreign studies had never reported an ADR, let alone on a continuous basis. The studies are silent on the frequency of reporting, for those who have reported. Also remarkable is result of the Irish study indicating that 90% of the respondents had diagnosed an ADR that they had not reported. The Dutch study had similar responses, ranging by practice group from 72% to 86% of respondents who had not reported diagnosed ADRs.⁸³

Unawareness of reporting systems does not seem to be the cause of underreporting. The percentages of doctors who admit to not knowing how to report ADRs to national health authorities is in the twenty per-

⁸²Landow, *supra* note 2 at 192.

⁸³Eland, *supra* note 60, at 624.

cent range. This would seem to explain why some doctors have never reported. However, in the Italian study, while seventy percent of its respondents claimed to know how to report ADRs to the agencies, a data analysis showed that the reporting rates were similar for those who claimed to be aware of the procedures and those who did not, indicating that lack of awareness may not be the driving force of non-reporting. Additionally, in many of the studies there were significantly more respondents who had never reported than those who claimed ignorance of how to report. After the 1993 publicity campaign, it is hard to believe that many doctors in the United States could still be unaware of MedWatch, regardless of how the awareness has affected their reporting habits. Therefore, while reporting is not yet habitual for physicians, it is probably not because they are unaware of the reporting system.

2.

Reporting biases

It has been suggested that spontaneous reporting is often subject to reporting biases, and these may reflect the fact that reporting is not habitual. Spontaneous reporting information is received in an uncontrolled and anecdotal way such that many factors can influence which types of reactions are more likely to be reported.⁸⁴ Some suggest that spontaneous reporting systems like MedWatch are inherently biased toward collecting certain reactions. For example, it makes sense that promotional claims, reports in the medical literature, and the media affect reporting.⁸⁵ If reporting were truly ingrained these would not seriously affect

⁸⁴See Landow, *supra* note 2, at 192.

⁸⁵See Stanley A. Edlavitch, Ph.D, *Adverse Drug Event Reporting, Improving the Low US Reporting Rates*, 148 ARCHIVES INTERNAL MED. 1499, 1500 (1988).

reporting habits. The length of time the product is on the market⁸⁶ and the publicity of other reactions to the drug also significantly affect reporting. Products that have been on the market for a long time may tend to be reported on less frequently since their reactions are assumed to be well known. Some of these disparities can be partially alleviated by making clear what should and should not be reported, and by inculcating reporting habits. This may increase reporting of all ADRs, not just those in the media, for example.

3.

Awareness of spontaneous reporting system benefits

The attitudinal studies cast doubt on whether medical professionals are aware of the importance of spontaneous reporting. Although the Italian study showed virtually no respondents stating that reporting systems are not valuable, the South African study had between 19 and 37% of its respondents essentially agreeing, depending on practice area. This data indicates that some physicians may not understand the value of reporting, which can certainly affect how they prioritize it.

Some practitioners do not know what purposes spontaneous reporting systems serve. For example, the respondents in the Italian study largely misunderstood the purposes of spontaneous reporting systems. Many (63.9%) thought they measure the incidence of ADRs, a function that they cannot effectively carry out. This may not be so meaningful given Italy's poor reporting history. However, doctors in the United Kingdom study also lacked a key insight into reporting. What particularly concerned the authors of the UK study was that a "high proportion of all doctor groups were unaware that yellow card data is used extensively

⁸⁶See Landow, *supra* note 2, at 192.

to compare the toxicity of drugs in a similar therapeutic class.”⁸⁷This overall ignorance of the benefits and purposes of spontaneous reporting systems hinders the ability of the systems to function efficiently.

4.

In whom is reporting ingrained?

It is noticeable that the reporting data varies largely between practice groups. The EU study data showed that fewer specialists than general practitioners, across the board, had ever reported ADRs. In the Dutch study, only 38% of the surgical specialists had ever reported ADRs, while the medical specialists and general practitioners’ responses were 68% and 64% respectively. Correspondingly, the surgical specialists in the Dutch survey were much less likely to be aware of the need to report ADRs. The surgical specialists in the South African survey claimed to have observed far fewer ADRs than the other two groups and understood the value of reporting the least, and none had ever reported an ADR.⁸⁸ About 70% of the respondents in the Irish study had reported an ADR at some point, but the rate was higher for the general practitioners than for the hospital doctors.⁸⁹ It is worthwhile to mention that the Dutch survey found that the age, gender and time since specialization did not show significant effects on the results.⁹⁰ These practice group variations may be telling as to where our attentions ought to be focused. If surgical specialists hardly see ADRs, which may be predictable, perhaps attempting to shift their attitudes about reporting is not as worthwhile as for those practitioners who often face ADRs. On the other hand, perhaps it may be best to particularly focus

⁸⁷Bateman, *supra* note 64, at 426.

⁸⁸Robins, *supra* note 66, at 131, 133.

⁸⁹Williams, *supra* note 58, at 257.

⁹⁰Eland, *supra* note 60, at 625.

on these groups who are under-informed because if they hardly see ADRs it may be because they tend to come across ADRs that are more rare. Also, if a whole practice area fails to report on a continuous basis, there will be a whole set of ADRs, those that arise in that particular medical field, for which there will not be reports. Therefore, it may be best to focus attitude-shifting efforts *especially* on those particular medical fields that do not report often and do not see so many ADRs. Further study into practice group distinctions would be meaningful in order to determine how to deal with these differences.

The reporting population can also be divided according to profession. Trends in reporting habits may be meaningful if physicians, pharmacists and nurses are analyzed separately. After MedWatch, the percent of reports from pharmacists increased from 56% to 70%, while the percent from physicians dropped from 22% to 15%.⁹¹ As an explanation for this shift, the study's authors hypothesized that physicians were reporting the events to the hospital pharmacists who, in turn, submitted the reports.⁹² Unfortunately, while the attitudinal studies focused on physicians, they did not solicit information about whether the responding doctors had ever assigned anyone in their medical staff to report an ADR. Also, since attitudinal studies have generally focused on physician reporting, it is hard to know how ingrained reporting is for pharmacists and nurses. These individuals may be a less-tapped audience for improving reporting rates, as reporters on their own initiative or as delegates for reporting.

⁹¹Piazza-Hepp, *supra* note 47, at 1437-38.

⁹²*Id.* at 1438.

5.

To whom do reporters report?

Those practitioners that do report ADRs vary in their preferences of reporting to a national agency or a pharmaceutical company. The data in the EU study showed that doctors across the European Union, with the exception of Italy, Portugal, and Ireland, tend to report to national agencies at a much higher rate than they report to the pharmaceutical manufacturers.⁹³ The Dutch and South African surveys revealed some telling distinctions between types of practitioners. In the Netherlands, the general practitioners preferred reporting to the national reporting center,⁹⁴ while the medical and surgical specialists preferred reporting to the pharmaceutical industry.⁹⁵ One wonders about the reason for such differences. Are medical specialists targeted more directly by pharmaceutical promotions, leading them to think of manufacturers automatically when they encounter adverse reactions? The authors of the study explained that medical specialists might report more often to pharmaceutical companies because those practitioners are more often involved in clinical trials with the companies.⁹⁶ In the South African study, a total of 64.5% of the respondents considered it necessary to advise an agency of an ADR, but significantly more medical specialists thought so (88.5%), with general practitioners and surgical specialists trailing at 52.5% and 68.5% respectively.⁹⁷ However, more general practitioners than other doctors favored informing the pharmaceutical representative about ADRs (GP:68%, MS:42%, SS:31.5%).⁹⁸ Ironically, these trends are not at all consistent with the Dutch figures, in

⁹³Belton, 52 EUR. J. CLINICAL PHARMACOLOGY at 424, *supra* note 49. It is worth noting that Portugal's national reporting system had only just been established around the time of the survey, therefore the survey data may not reflect a real preference to report to manufacturers. *See id.* at 426-27.

⁹⁴Eland, *supra* note 60, at 624.

⁹⁵*Id.*

⁹⁶*Id.* at 625.

⁹⁷Robins, *supra* note 66, at 131-32.

⁹⁸*Id.* at 132. The questions here asked "Do you consider it necessary to advise any outside agency of an ADR and, if so, whom?" and "Do you tell the pharmaceutical representatives about the ADR" (usually yes or usually no). *Id.* at 132. Because neither question solicited direct data about whether the individual respondents had reported to either of these groups, I did not include their responses in Table 1 under those titles. However, the results do seem to have some illustrative value.

which the general practitioners preferred reporting to the health authority but the other two groups preferred reporting to the manufacturer. It is certainly not clear whether there are coherent preferences based on professional specialty. However, such trends may signify differences in why doctors find reporting important and to whom they feel they have a duty to report. These attitudinal variations may have the potential to clarify reasons for underreporting.

6.

How can we make reporting more ingrained?

a.

Informative advertising

In the United States, more “advertising” is not likely to dramatically change reporting habits. Any informed doctor or other medical health practitioner should have noted the 1993 modifications since they were prevalent in the medical literature. If the barrage of MedWatch information in 1993 had only a limited impact on doctors, it is logical to assume that additional advertising efforts will only have marginal benefits except in informing new doctors. Medical school students may be the only meaningful beneficiaries of informational efforts to inculcate the importance of reporting adverse events.

b.

Mandatory reporting by physicians

It does not seem clear that requiring health care practitioners to report adverse reactions would have any significant effect on reporting rates. France, Sweden, Norway and Italy all mandate reporting but their reporting rates are still low.⁹⁹ Interestingly, about 20% of respondents in the Italian study said that the legal requirements mandating reporting were a factor in deciding to report.¹⁰⁰ This is relevant in assessing whether mandating reporting would be valuable, since it indicates that a sense of legal obligation encourages reporting. Despite that statistic, perhaps the most significant reason for the ineffectiveness of mandating reporting is that the standards of what needs to be reported are simply too ambiguous to give effect to a mandatory adverse reaction reporting system. Since it is not often clear whether the reaction was caused by the drug, it would be very hard to insist upon reporting, and even harder to enforce such a system. If non-reporters were subject to criminal or civil penalties a mens rea requirement would be hard to fulfill in many cases where the drug and reaction were not clearly linked. How causally linked must they have been in order to establish that a doctor knew she should have reported but did not? It is not clear that an attempt at such enforcement is the best use of our resources. Moreover, requiring reporting would attach an even greater negative stigma to the process than already exists, particularly if non-reporters were subject to criminal penalties or civil damages.

At this point what is most lacking is a feeling of ethical or moral obligation to report out of a sense of necessity or importance. The MedWatch program is not simply a repository of useless paperwork; it serves an important social goal. Requiring reporting by attaching a hypothetical threat to not reporting may seriously harm the attitudes of medical professionals by creating a negative association with reporting, while being unable to achieve the desired result. Attempting to dissolve the obstacles to voluntary reporting and

⁹⁹ See Robins, *supra* note 66, at 134; Cosentino, *supra* note 55, at 85.

¹⁰⁰ Cosentino, *supra* note 55, at 86.

continuing to instill a sense of obligation or duty would likely be more successful than mandating reporting.

c.

Conclusions

While neither of these mechanisms seem particularly effective in further ingraining reporting in physicians, it is not clear that lack of inherent tendency to report is really the biggest limit to the quantity of reports being filed. The rest of this article will discuss other potential obstacles to frequent reporting. Furthermore, even a relatively low percent of reporting can be very useful if it provides the desired information. Perhaps improvement efforts targeted at report quality, discussed in the upcoming section, would be more useful than those targeted at report quantity.

B.

How selective and comprehensive is reporting?

While the quantity of reports received by a spontaneous reporting system is important, the quality of those reports is equally important. The quality assessment has two parts. The first is whether the reaction should have been reported at all. For example, the MedWatch system solicits serious and unexpected events only. The fraction of reports that meet the desired reporting qualifications determines how “selective” a system’s reports are. The second part of the qualitative assessment is whether the report includes the essential information. Reports should include the patient’s baseline status, medical history, laboratory and clinical data

in support of the event diagnosis, and the duration of the drug therapy.^{101, 102, 103} This second qualitative element can be described as “comprehensiveness.”

1.

The studies

The data shows that many physicians are generally aware of what reactions should and should not be reported. Overall, the physicians in the studies displayed in Table 1 seemed to understand the major reasons for reporting ADRs, with the notable exception of those in the Italian study. Only about 58% of the doctors in the Italian study correctly identified that according to Italian law *all* suspected reactions to any drug on the market should be reported.¹⁰⁴ Furthermore, less than 40% of the Italians surveyed agreed with any of the propositions about why to report: unusualness of the reaction, severity of the reaction, or involvement of a new drug. However, given that the Italian study focused on an area with minimal reporting, this may not be shocking. An American study did find significant selectivity improvements when it analyzed reporting data before and after MedWatch, focusing on 1992-1994.¹⁰⁵ The results showed that the percentage of reports that were serious increased from 34% to 49%, advancing MedWatch’s selective reporting goal.¹⁰⁶ The efforts to clarify what should be reported seem to have been useful. For example, the MedWatch Voluntary Reporting Form lists what is “reportable” in very user-friendly terms and this type of additional guidance may have

¹⁰¹ See Piazza-Hepp, *supra* note 47, at 1438.

¹⁰² It is unlikely that patients will report concomitant use of alcohol or sedative-hypnotic agents even if they are used. See Shader, *supra* note 38, at 303.

¹⁰³ Critics assert that MedWatch does not ask enough relevant questions. It does not explicitly ask about the use of over-the-counter drugs, vitamins, or health and dietary supplements, all of which are important in explaining adverse events. See *id.*

¹⁰⁴ Cosentino, *supra* note 55, at 87.

¹⁰⁵ Piazza-Hepp, *supra* note 47 at 1438.

¹⁰⁶ *Id.* at 1437-38.

been critical in enhancing selectivity.¹⁰⁷

It appears that the selectivity of reports is somewhat related to where they are submitted. A pre-MedWatch study in the United States showed that reports submitted directly by physicians to the FDA had a higher proportion of serious reactions (30%) than manufacturer-submitted reports (18%).¹⁰⁸ The data is stark in an earlier study, in 1970, which showed that although physicians directly reported only 1% of the total reports, they identified 24% of all the ADRs that resulted in labeling changes that year.¹⁰⁹ A United Kingdom study in 1983 found that physician-direct reports led to the investigation of 72% of the most serious ADRs since the thalidomide crisis in the early 1960's.¹¹⁰ These figures indicate that physicians do have a fairly accurate ability to determine which reactions are more significant, and they may tend to report them directly to the spontaneous reporting systems.

However, while some physicians know the fundamentals, they seem to be unaware of important details on what should be reported. For example, 27.2% of the doctors in the Dutch study would not report an ADR if the patient had purchased the drug over the counter.¹¹¹ The reasons for this are unclear. This may reflect assumptions that the reactions must be too well known to report or that over-the-counter drugs must be safe. Regardless of why they do not report these, this is evidence of a misunderstanding about reportable ADRs. Another example of this type of misunderstanding is in the United Kingdom. In the EU-UK¹¹² survey, participants were specifically asked whether they knew the significance of the black triangle symbol that appears in various places, including advertising literature for new products.¹¹³

¹⁰⁷See MedWatch Voluntary Reporting Form, App. B.

¹⁰⁸Faich, 151 ARCHIVES INTERNAL MED. at 1647, *supra* note 17.

¹⁰⁹H. Denman Scott, MD et al., *Physician Reporting of Adverse Drug Reactions*, 263 JAMA 1785, 1785 (1990).

¹¹⁰See *id.* at 1785-86 (citing to G. R. Venning, *Identification of adverse reactions to new drugs, II: how were 18 important adverse reactions discovered and with what delays?*, 286 BRIT. MED. J. 365 (1983)).

¹¹¹Eland, *supra* note 60, at 625.

¹¹²The United Kingdom segment of the European Union study

¹¹³Belton, 39 BR. J. CLINICAL PHARMACOLOGY at 225, *supra* note 54.

The black triangle symbol means that the CSM is paying specific attention to the medication and wants enhanced reporting of all ADRs, not just serious ones. This symbol is generally used with new products.

If you see the black triangle symbol

against a product entry in the British National Formulary (BNF), MIMS, the ABPI Compendium of Datasheets and Summaries of Product Characteristics and advertising material, this indicates that the [Committee on Safety of Medicines]/[Medicines Control Agency] are intensively monitoring that product. A black triangle will be assigned to a product if the drug is a new active substance. However, a product containing previously licensed active substances may also be monitored if it meets one or more of the following criteria:

- a new combination of active substances;
- administration via a novel route or drug delivery system;
- a significant new indication which may alter the established risk/benefit profile of that drug.

This last criteria has recently been added at the request of the CSM.

The CSM/MCA wish to receive all suspected ADRs associated with these products in order to confirm the risk/benefit profile established during the pre-marketing phase. The black triangle drugs are monitored closely for a minimum of two years and the black triangle symbol is not removed until the safety of the drug is well established.

Committee on Safety of Medicines web page, accessible through <http://www.open.gov.uk> (last accessed April 6, 2001). In total, 64% of the respondents correctly identified that the symbol meant that all suspected reactions to the product should be reported. However, only 48% of those surveyed knew that the symbol indicated a new drug, and only 39% knew both facts.¹¹⁴ Also, the general practitioners were better informed about the black triangle classification than the hospital doctors.¹¹⁵ Similarly, in the UK-only study, as in the EU-UK study, a very high proportion of doctors, especially the hospital doctors, were unfamiliar with the purpose of the CSM's black triangle symbol. Therefore, many physicians lack knowledge of certain critical details of ADR reporting.

The quality of reports, as determined by rates of inclusion of important information, was generally higher after MedWatch.¹¹⁶ One factor that is important in assessing comprehensiveness is who is doing the reporting. Post-MedWatch, both pharmacists and physicians report the proper information equally, with the exception of the patient's medical history.¹¹⁷ The fact that pharmacists have limited access to patient histories may explain why they include them less often. Given the overall high quality of pharmacist reports, perhaps efforts to enhance their reporting tendencies would be beneficial.

While medical professionals have a general understanding of what to report, efforts to increase their understanding of the details of individual reporting systems may be valuable. Methods for improving selectivity

¹¹⁴Belton, 39 BR. J. CLINICAL PHARMACOLOGY at 225, *supra* note 54.

¹¹⁵*Id.*

¹¹⁶Piazza-Hepp, *supra* note 47, at 1437-38.

¹¹⁷*Id.* at 1438.

are discussed in the next section. Comprehensiveness is less of a concern given that the details of what ought to be reported can be neatly summarized on reporting forms. Given that the only clear way to improve this is through educational efforts, other options for improving comprehensiveness will not be discussed in the next section.

2.

How can selectivity be maximized?

As always, education can be cited as a mechanism for improving selectivity, particularly for those areas of reporting which are misunderstood. However, although it may be useful to improve overall selectivity, perhaps what would be most valuable would be to target efforts so as to maximize the combination of quantity and selectivity. This would involve increasing reporting for certain medications, those that we generally have difficulty learning about. Particularly with uncommonly prescribed medications, it seems that a significant delay in discovering adverse reactions could be avoided with increased targeted reporting driven by media campaigns.

a.

Targeting through reporting requirements

Adoption of a targeted reporting system like that of the United Kingdom could significantly enhance the selectivity of reports without creating ambiguity as to what needs to be reported. This would somewhat

eviscerate the need for an overall increase in reporting. The United Kingdom places a black triangle symbol, \blacktriangle , on medications in which the Committee on Safety of Medicines is particularly interested. While the United Kingdom uses this symbol only for medications that have been on the market for less than two years, there is certainly the potential to use it more flexibly. For example, it may be possible to collect data more quickly on obscure medications if the symbol were also put on them. If higher reporting rates would only really be beneficial for those medications that are not used in quantity (because no significant amount of time until discovery of ADRs would be saved for the others), this might be a sensible option. This strategy would focus attention on those medicines that are of particular concern, while continuing the inflow of information about other drugs to monitor them for unforeseen reactions. However, it is clear that a new regime such as this would require a significant awareness campaign so as to avoid the situation in the United Kingdom where doctors are not familiar with the symbol and its meaning.

b.

Targeting through questionnaires

One useful method for compiling adverse reactions is sending questionnaires to medical practitioners. A 1977-78 New Zealand study tried to determine the reasons for the cessation of therapy with certain medications.¹¹⁸ The study monitored specific new drugs, which were dispensed only from hospital pharmacies, throughout the first year of their release.¹¹⁹ In an effort to determine why doctors would cease therapy with the drugs, the researchers sent questionnaires to the prescribing doctors after it was clear that their

¹¹⁸D. M. Coulter, MB, ChB, DTM & H, *Study of Reasons for Cessation of Therapy with Perhexiline Meleate, Sodium Valproate and Labetalol in the Intensified Adverse Reaction Reporting Scheme*, 93 N.Z. MED. J. 81 (1981).

¹¹⁹*Id.* at 82.

patients were no longer taking the medications.¹²⁰ The response rate to the questionnaires was 81 percent.¹²¹ The results showed that often an adverse event had caused the termination of use.¹²² Moreover, the information received from the questionnaires did not duplicate that which had already been received through spontaneous reporting.¹²³ Events reported spontaneously were a less select group of events and did not always result in termination of the drug's use.¹²⁴ This surveying increased the yield of adverse events about these medications by almost 100%.¹²⁵ The study concluded that "examination of reasons for cessation of therapy is a useful adjunct to spontaneous reporting of adverse events," especially for drugs being monitored intensively.¹²⁶ This type of system, while costly, can be used to monitor medications that are of particular concern. This would allow increased attention to certain suspect medications without detracting from spontaneous reporting of other drugs.

C.

Uncertainty of the cause of a reaction interferes with reporting

Some reaction causes are inherently difficult to identify. Since many patients take multiple drugs it is particularly hard to identify which drug caused a reaction and whether the combination itself caused it. As Dr. Glen Griffin put it in his article in *POSTGRADUATE MEDICINE* urging people to report, "[s]ince many people are taking more than one medication at a time, the opportunities for unanticipated drug reactions

¹²⁰ *Id.*

¹²¹ *Id.*

¹²² *Id.* For the three medications, Perhexiline, Valproate, and Labetalol, adverse events were stated as the reason for cessation of therapy in 20%, 15% and 43% of the cases respectively. *Id.*

¹²³ *Id.* at 83-84.

¹²⁴ *Id.*

¹²⁵ *Id.*

¹²⁶ *Id.* at 81, 84.

become mind-boggling.”¹²⁷ This, of course, results in a hesitancy to report, as revealed in the South African study in which an overwhelming number of doctors included multiple medications as an important factor in explaining underreporting.¹²⁸ Also, adverse reactions with long latency or those that produce unusual symptoms are not quickly even recognized as ADRs.¹²⁹ The time delay of some reactions and oddness of others can make their causes seem very uncertain, especially if the patient has been on multiple medications. Although there does not seem to be an easy solution to these problems, reporting systems could encourage doctors to report these uncertainties nonetheless. It may be preferable to receive reports about adverse reactions attributable to one of a few drugs than not to receive them at all. This may also aid in highlighting adverse reactions caused by drug interactions.

Other evidence of uncertainty concerns is found in the South African study where over ten percent of the participants agreed that the concept of a “drug event” rather than a “drug reaction” would have a better reporting response because it does not directly “incriminate” the drug.¹³⁰ This anxiety is probably correlated with a reluctance to commit to a conclusion when there is insufficient evidence of an ADR. Shifting from a drug reaction system to a drug event system essentially decreases the blame on the drug because it allows for the possibility of errors leading to the adverse event. This distinction, while sensible on paper, seems wholly linguistic. Unless a doctor knows that the suspected drug event was caused by human error of some nature, he would normally report it as a suspected adverse drug reaction. And if the doctor does have reason to believe that the event was caused by human error, it is questionable whether reporting it would be valuable to a spontaneous reporting system. Therefore, other than dissolving mental uncertainty barriers to reporting, the shift from ADRs to ADEs may not be more useful than emphasizing that medical professionals

¹²⁷Glen C. Griffin, MD et al., *Report Every Adverse Drug Reaction! We're all in this together*, 101 POSTGRADUATE MED. 13, 14 (1997).

¹²⁸See Robins, *supra* note 66, at 133.

¹²⁹See Edlavitch, *supra* note 85, at 1500.

¹³⁰Robins, *supra* note 66, at 133, 134.

need only *suspect* that the drug caused the reaction.

D.

Medical health practitioners do not have time to report

1.

Time is a limitation to reporting

Undoubtedly one of the biggest reasons for underreporting is that the modern physician is faced with temporal and economic pressures such that it may not seem worthwhile for him to spend time reporting. The information in Table 1 suggests that time may be a big factor in reporting rates. Furthermore, in the UK study, in those areas with low reporting rates, the doctors seemed to be spending more time in actual contact with the patients,¹³¹ suggesting that there may be some correlation between time and reporting rates.

It is worth questioning the reasons behind the balance in priorities that has been struck. Is it really better to spend the extra thirty minutes¹³² with patients or spend the time reporting an adverse reaction? For the

¹³¹Bateman, *supra* note 64, at 425. Additionally, there was less of an appreciation for the benefits of the Yellow Card system in the low reporting areas, which lends support for the conclusion that the physicians' level of appreciation affects the priority of reporting.

Interestingly, the general practitioners and junior hospital doctors in the low reporting areas wrote more prescriptions in comparison to the doctors in the higher reporting rate areas, so those in the low reporting areas probably diagnosed more ADRs. *Id.*

¹³²The MedWatch form states "The public reporting burden for this collection of information has been estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information." MedWatch Voluntary Reporting Form, App. B.

individual patient the former is preferable, but for society, the latter may be preferable. To whom is the doctor's duty? It is clear that cost-benefit decisions must occur in these prioritization situations, but who makes them and are they knowingly made?

The medical culture of this decade has emphasized the economics of health care, leading to changes in the way doctors provide medical care. Doctors are limited in the amount of time they can spend with patients, and most doctors would probably prefer to spend the time with the patient who has suffered an adverse reaction rather than on describing the occurrence on a form. The FDA's position of already limiting reporting to what is serious and new suggests a policy decision that patient time should not be wasted on what we already know; only information that would significantly aid the community is worth the temporal sacrifice.¹³³ The diverging interests with which doctors struggle parallel the legal services lawyer's ethical dilemma: whether to spend time representing a client in a "small" case or spend their time working on a law reform project which will affect hundreds of people. There is some duty to do both, which creates difficulty since time is limited. Moreover, many doctors are stuck in the middle of another balance: working for their patients and their employer HMOs, two groups that put diverging pressures on physician time. In this light, it is easier to understand their predicament and harder to decide what course of conduct they should choose.

¹³³Of course, the FDA policy of only soliciting certain reports may have more to do with FDA resources than with physician time, so it may still be worth analyzing whether the overall social benefit from broader reporting outweighs the social cost in terms of physician time.

2.

Changing the priority balance

Among the options for changing this priority balance and non-reporting attitudes is providing incentives for reporting. Clearly this would only be preferable if we find the present balance undesirable. To the extent that the current balance results from economic pressures to serve more patients, an incentive system may have some weight in changing it. The United Kingdom study, which actually asked respondents whether they felt they should be compensated for their time, indicates that this might be promising.

It is possible that an incentive structure will pass reporting procedures into the hands of other health care professionals or staff members, whose time, although also valuable to the patient, may be preferable to donate to this cause. Depending on the complexity, it may not be too difficult for staff members to provide most, if not all, of the relevant reporting information by getting a summary from the doctor and looking through a patient's file.¹³⁴ Much of the information currently required by the FDA does not require thorough medical knowledge.

Perhaps the biggest impediment to creating an incentive based system is that no single group or actor bears the brunt of the billions in annual costs created by toxic effects of medications. While in sum it may be economically beneficial and more efficient to prevent adverse reactions through a mechanism like an incentive system, it may not be in any individual group's interest to take that financial responsibility. The costs of adverse reactions are currently spread among various groups: patients, the government, insurance companies, and pharmaceutical companies, to name a few. It is, nevertheless, valuable to consider the possibility of incentive programs since if they were worthwhile, financial backing could possibly be achieved through joint ventures or other means.

¹³⁴See Williams, *supra* note 58, at 260 (suggesting that nurses could take over some reporting duties).

One possible system for financial incentives would give doctors or their employers a monetary “reward” for reporting adverse drug reactions. The first question is who would provide this reward? Both pharmaceutical companies and insurance companies may have some economic reasons to participate in such a system since they each bear significant costs from adverse reactions. Pharmaceutical companies have been paying enormous tort damage awards to consumers who have been seriously adversely affected by their products. Insurance companies face daily hospital bills from adverse reactions. Depending on the costs of implementing an effective system like this, it may be more efficient to prevent these reactions and the subsequent lawsuits and hospital bills by discovering problems earlier. Both groups stand to gain if ADRs are prevented in the first place. Of course, even if this is true, it is somewhat perverse to expect pharmaceutical companies to pay doctors to give them distressing information about problems with their drugs. The second question is to whom would the reward be paid? If it were paid directly to the doctors, it may affect their attitudes but may not change the priorities in the environment where they work. If it were paid to health organizations employing doctors, it may result in a more pro-reporting environment but may have less of a direct effect on the doctors’ individual attitudes.

One Irish study actually attempted to stimulate reporting by using a fee.¹³⁵ The study, published in 1990, offered junior doctors at a hospital three Irish punts (equivalent to about 4.5 United States Dollars at the 1990 conversion rates)¹³⁶ if they completed yellow cards (reporting forms).¹³⁷ Collection of the reports for six weeks showed a dramatic increase in reporting. The incentive “increased the rate of reporting almost 50-fold.”¹³⁸ Forty eight percent of the doctors in the survey reported reactions, compared to the baseline 10%

¹³⁵John Feely et al., *Stimulating reporting of adverse drug reactions by using a fee*, 300 BRIT. MED. J. 22 (1990).

¹³⁶The historical conversion rate was determined from data found at <http://www.ozforex.com.au/home.htm?http://www.ozforex.com.au/newhome> (last accessed April 9, 2001).

¹³⁷Feely, 300 BRIT. MED. J. at 22, *supra* note 135.

¹³⁸*Id.* at 23.

figure. Random testing showed confirmation of the adverse reactions in over ninety percent of the cases.¹³⁹ Of the forty doctors that reported, thirty-two said that the fee was an incentive to report. Unfortunately, after the study was complete and the payments stopped, the number of reports fell dramatically.¹⁴⁰ This effort seems to show that an incentive system can be meaningful. It is surprising how small a fee was effective in this study. Perhaps the fee was more of a reminder to the doctors than an incentive. It would be interesting to know if reporting rates would have continued to be high during a longer-term period given that the monetary compensation was minimal.

a.

Ethics and the Law

If pharmaceutical companies establish a “reward” system like this, there may be serious ethical concerns. However, it is not clear that this would fall outside the boundaries dictated by medical ethics. The American Medical Association Ethical Guidelines for doctors seek to prevent pharmaceutical companies from “owning” doctors. Gifts from the industry to physicians are limited to those that entail a benefit to patients and are not of substantive value.¹⁴¹ The key question is whether a reporting incentive is even a gift under the guidelines. If it is a “payment” which is proportional to the task done and benefit provided, it is arguably not a gift. More broadly however, the question is one of making the physicians indebted to industry. Guideline 6, on gifts from industry, adequately summarizes this concern. “No gifts should be accepted if there are strings attached. For example, physicians should not accept gifts if they are given in relation to the

¹³⁹ *Id.*

¹⁴⁰ *Id.*

¹⁴¹ American Medical Association E-Addendum II: Council on Ethical and Judicial Affairs Clarification Gifts to Physicians from Industry (E-8.061) available at http://www.ama-assn.org/apps/pf_online/pf_online?f_n=browse&doc=policyfiles/CEJA/E-002.0.HTM&&s_t=&st_p=&nth=1&nxt_pol=policyfile (last accessed April 6, 2001).

physician's prescribing practices."¹⁴² Regardless of whether or not these incentives are accurately defined as "gifts," doctors receiving routine payments from industry raises legitimate conflict of interest concerns. In Britain, the Royal College of Physicians studied the physician-industry relationship. It published a report that emphasized the importance of a close relationship for the treatment of patients and the assessment of new drugs, but at the same time emphasized the need for doctors to be impartial and honest.¹⁴³ "The overriding principle is that any benefit in cash or kind, any gift, and hospitality, or any subsidy received from a pharmaceutical company must leave the doctor's independence of judgment manifestly unimpaired."¹⁴⁴

The Federal Medicare and Medicaid Anti-kickback statute also influences the legality of this proposal. The Department of Health and Human Services Office of Inspector General released a "Special Fraud Alert" on Aug. 23, 1994 specifying certain practices that could result in an investigation. "If just one purpose of a marketing scheme is to induce the prescription of a drug reimbursable by Medicaid, then the criminal anti-kickback statute is implicated and the physician, pharmacy, or supplier receiving payment could be subject to criminal prosecution and exclusion from Medicare and Medicaid."¹⁴⁵ This was intended to prevent risk from doctors whose judgment may be impaired by payments.¹⁴⁶ It seems unavoidable that a system like the one proposed above would conflict with the language of this alert. Rewards for reporting adverse reactions are probably a form of "marketing scheme" and would likely induce changes in prescribing behavior. Still, because of the possibility of creating exceptions to the ethical rules and kickback laws, it may be valid to question the assumption that, in sum, this would be detrimental to patients.

¹⁴²*Id.*

¹⁴³See Fred Rosener, *Ethical relationships between drug companies and the medical profession*, 102 AM. C. CHEST PHYSICIANS 266 (1992).

¹⁴⁴*Id.* (summarizing the British report).

¹⁴⁵See *Fraud Alert Outlines Potentially Illegal Prescription Drug Marketing Activities*, BNA HEALTH CARE DAILY, Aug. 24, 1994 (citing to the Department of Health and Human Services Office of Inspector General 'Special Fraud Alert').

¹⁴⁶See *id.*

b.

Prescribing Habits

An incentive system may lead doctors to prefer one company's drug to another's. If the amount of "reward" were left to the pharmaceutical company's discretion, the conflict of interest concerns associated with other "gifts" would remain because companies could vie for the selection of their products by offering the highest rewards. But if there were one standard amount for this reward, it would significantly preempt much of the conflict of interest since competition over reward values would not exist. Of course, this fixed rate would probably have to be statutorily permitted in order to overcome the anti-kickback statute as well as any antitrust issues. Additionally, competition would be most effectively "stifled" if all of the pharmaceutical manufacturers participated. Otherwise, incentives would still exist for favoring one product over another. Practically speaking, this concern is of little significance. In order for an optional system to work, it must be in industries' financial interests to pay this reward for information that will save them millions in litigation costs. If that is correct, there is a strong incentive for all companies to participate. Moreover, the risk of having another company sway prescription habits will also create this incentive. Finally, any concern about small businesses not being able to compete with industry giants because of financial limitations may not be realistic in a market composed largely of giants. These small actors, if they cannot afford a more efficient system, will be those who likely cannot afford to compensate the tort victims, and to the extent they are selected out of the market, it may be in accordance with society's policy choices favoring tort compensation. Nevertheless, it is not clear that it is desirable to further increase the entry costs into the pharmaceutical market, especially if a system like this essentially "forces" smaller companies to pay a reward even if for

them it is not economically preferable to paying tort damages.

Still, if an incentive system is at all effective, prescribing habits will necessarily change. Since newer drugs are more likely to have adverse reactions, and therefore result in more “rewards,” there is a risk that that this type of incentive may have some subconscious swaying effect in choosing between two “equivalent” medications. Already physicians are pressured by patient and doctor advertising to prescribe newer medications. In an editorial published in the *JOURNAL OF THE AMERICAN MEDICAL SOCIETY* Dr. Alastair Wood wrote “[p]hysicians have a major role in the prevention of adverse drug reactions and should resist marketing pressures to prescribe new and potentially more toxic drugs in preference to prescribing well-established safer drugs.”¹⁴⁷ One result of a bias toward newer drugs is that while short-term adverse reactions will be more quickly reported due to increased reporting and a higher sample size, longer-term adverse reactions will affect a larger number of people if new medications are more often prescribed. It would be important to factor in this cost when determining the desirability of an incentive structure.

The problems would be similar if insurance companies or even the FDA took on the task of administering an incentive program. However, some of the ethical concerns would be diminished, particularly if the Food and Drug Administration established such a program. It does not seem that the ethical concerns would be substantially reduced if a health organization were receiving the reporting fee and not the doctor individually. The bias simply would be transferred to the organizational level. In all of these cases the problem of creating undesirable prescribing habits favoring riskier medications would remain, so in the end the increased reporting may not be worth the increased risks, even if this were financially feasible.

¹⁴⁷Alastair J.J. Wood, MD, *The Safety of New Medicines: The Importance of Asking the Right Questions*, 281 *JAMA* 1753, 1754 (1999).

3.

Note on reporting facility improvements

American physicians may not be aware of how easy reporting has become with the recent advent of web reporting. The option of online reporting may be more convenient than paper or phone reporting, however there has been no wave of media attention to this alternative, so many may not know of its existence. Therefore publicity about Internet reporting may be worthwhile.

E.

Liability concerns stifle reporting

1.

Is liability really a concern and why?

Despite the data in Table 1 suggesting otherwise, there is reason to believe that the liability factor may play a role in stifling reporting. Some studies in the United States have shown higher rates of concern for liability from reporting. The Food and Drug Administration itself, in proposing new regulations on adverse event report confidentiality, cited to studies that show a reluctance to report due to liability concerns.

It is well recognized that many physicians are concerned about the potential for involvement in litigation by their patients or third parties. In a 1992 survey of physicians regarding adverse event reporting, over 37 percent of the respondents agreed with the statement that reporting increases the risk of becoming involved in litigation; 18 percent of the respondents listed fear of becoming involved in the administrative or legal process as an important reason for not reporting adverse reactions. Several other surveys have been conducted which asked physicians what factors influenced their decision not to report an adverse event. Between 8 and 14 percent of the respondents in the studies stated that concern over legal liability was one reason why they did not report an adverse event.¹⁴⁸

If it is true that liability really is more of a concern to medical professionals than is apparent from the attitudinal studies in Table 1, one might wonder why that data does not reflect this. It is worth noting that none of the studies compiled were performed in the United States, and those countries' liability systems may be different than that of the United States. Moreover, the United States is a particularly litigious country, which may make the threat of litigation far more tangible. However, to my knowledge, none of the countries in the studies insulate their reporting physicians from malpractice liability, so the numbers still seem surprisingly low despite cultural and legal differences.

Not all the data in the compiled studies points as sharply to the conclusion that liability is not an issue in underreporting. One interesting finding of the Dutch study, from a question not posed in the other studies, was that 31.7% of the respondents would not report an ADR if another physician had prescribed the medication.¹⁴⁹The study did not attempt to explain this statistic. Of the possible explanations for this, a few seem to be particularly likely. Limited information about the patient's medical and medicinal state at the time of prescription could create more uncertainty about the cause of the reaction, leading the new doctor to refrain from reporting it. However, in many cases it is not clear that this complication is present. Often, if the patient had only recently begun using the medication, as is likely given that long-term reactions are rarely identified as ADRs, the medical history of the time of prescription will not be so outdated. This 31.7% statistic may reflect a disinclination to point "blame" on a different doctor, regardless of legal liability issues.

¹⁴⁹Eland, *supra* note 60, at 624-25.

Yet it seems incongruous that over thirty percent of doctors will not report ADRs if they did not prescribe the medication, but only 2-3% of the same group claim that legal liability is a factor in underreporting. Undoubtedly the desire not to point fingers is substantial, but is it so great that it causes such a discrepancy, or, perhaps, is the 2-3% figure lower than reality? In other words, when it comes to legal liability, do people more quickly deny that it is a personal concern but worry about creating it for others? If so, why? Further liability disquiet comes from the authors of the EU study, who, while admitting that the data did not indicate that legal liability created a large reluctance to report, warned that “in an increasingly litigious age, national agencies might need to be prepared to be able to provide some reassurance to reporters that the information that they provide will not be used against them, personally, in any legal action.”¹⁵⁰ Finally, although a surprising 85-88% of the responding doctors in the UK study stated that they were happy to disclose their identity in submitting reaction reports,¹⁵¹ it does not necessarily follow that the disclosure of identity is not a disincentive to reporting some ADRs. If doctors only report those ADRs that do not make them uncomfortable for causation reasons, then disclosure will not be a concern.¹⁵²

It may also be that physicians are simply not aware of the effect the avoidance of liability has on their behavior. Admitting that a factor like lack of time stifles reporting reflects a somewhat calculated judgment on the part of the medical professional that ADR reporting is not as much of a priority as other things. However, to the extent that doctors recognize the benefits of the spontaneous reporting systems, and a large number seem to, it may be very difficult for them to admit, even to themselves, that they would be willing

¹⁵⁰Belton, 52 EUR. J. CLINICAL PHARMACOLOGY at 427, *supra* note 49.

¹⁵¹Bateman, *supra* note 64, at 426.

¹⁵²There is one piece of data that sheds light on the extent to which liability concerns are central in physician's thoughts. The Dutch study data showed that 27.2% of the doctors would not report ADRs from over the counter medications. Eland, *supra* note 60, at 625. However, these cases may be among the few where legal liability is the least implicated, if, for example, the patient purchased the drug over the counter without the doctor's recommendation. While this neither negates nor supports the argument that liability concerns are significant deterrents to reporting, it does indicate that they are not the only major concerns.

to forego those benefits in order to avoid liability. Though individual doctors may be reluctant to recognize how much potential liability shapes primary behavior, perhaps its greater effect is to create an atmosphere where reporting is not encouraged. Although individual doctors may not be aware of liability issues, many administrators are, and they have some influence in setting doctors' priorities. Consequently, they seem to have some ability to encourage reporting. It would be interesting to know how much encouraging they do and whether they feel it is in the hospital or facility's best interests to report. It may be telling that in both of the United Kingdom studies, the general practitioners knew more about reporting than the hospital doctors. Perhaps there is an attitudinal difference within their work environments that changes the value they place on reporting. Perhaps hospital doctors being less informed about reporting is a product of general institutional policies that try to avoid liability. In the United States, the Joint Commission on Accreditation of Healthcare Organizations requires that all hospitals "develop a system to summarize adverse drug reactions, to observe for trends that occur in in-hospital patients or outpatients in affiliated clinics, and to conduct ongoing drug utilization monitors."¹⁵³ This requirement seems like an effort to instill a pro-reporting environment since "ongoing accreditation of a health-care organization can be threatened if it does not have an active reporting program."¹⁵⁴

2.

The law in the United States

¹⁵³Linda M. Lucas, MD & Colleen A. Colley, PharmD, *Recognizing and Reporting Adverse Drug Reactions*, 156 W. J. MED. 172, 174 (1991).

¹⁵⁴David R. Witmer, PharmD, Fern Z. Liang, M.P.H., J.D., *Reporting of adverse drug reactions and physician liability*, 49 AM. J. HEALTH-SYS. PHARMACY 538, 544 (1992).

In July of 1995, the Food and Drug Administration passed a new regulation, 21 C.F.R. §20.63(f) about the confidentiality of adverse event reports.¹⁵⁵ The regulatory structure as it is currently set up essentially allows the public disclosure of adverse event reports submitted directly to the FDA but requires deletion of the names and identifying information of the patient and any third parties mentioned in the report.¹⁵⁶ The names of voluntary reporters or anyone associated with an adverse event shall not be disclosed by the FDA or a manufacturer in response to “a request, demand, or order.”¹⁵⁷ However, three exceptions apply. First, if both the voluntary reporter and the person who experienced the adverse event consent then the identities may be disclosed.¹⁵⁸ The second exception states that “[i]dentities of the voluntary reporter and the person who experienced the reported adverse event may be disclosed pursuant to a court order in the course of medical malpractice litigation involving both parties.”¹⁵⁹ This effectively means that in a malpractice case, an adverse event report is discoverable by a court order if the litigation involves the voluntary reporter and the person who experienced the adverse event. Interestingly, this suggests that it may be possible to bypass this disclosure in a malpractice case targeting the prescriber of the medicine if someone other than the prescriber files the adverse event report. Finally, the third exception is that the report, excluding the identities of any other individuals, shall be disclosed to the person who is the subject of the report.¹⁶⁰ The regulation also preempts any state or local law that “permits or requires disclosure of the identities of the voluntary reporter or other person identified in an adverse event report.”¹⁶¹ Additionally, this regulation does not prevent disclosure of reports (and all of the personal information within them) by others who may be in possession of copies of them, including the voluntary reporters, other medical personnel or hospitals.¹⁶²

¹⁵⁵21 C.F.R. §20.63(f).

¹⁵⁶ See 21 C.F.R. §20.111(c)(3); Bonnie L. Mayfield, *Preventing Manufacturer Compelled Disclosure of Confidential Information Contained in Voluntarily Submitted Adverse Event Reports*, 19 AM. J. TRIAL ADVOC. 265, 265 (1995).

¹⁵⁷21 C.F.R. §20.63(f).

¹⁵⁸ See 21 C.F.R. §20.63(f)(1)(i).

¹⁵⁹21 C.F.R. §20.63(f)(1)(ii).

¹⁶⁰ See 21 C.F.R. §20.63(f)(1)(iii).

¹⁶¹21 C.F.R. §20.63(f)(2).

¹⁶² See Mayfield, *supra* note 156, at 271-72.

While the FDA seems to agree that subjecting doctors to potential liability will jeopardize reporting,¹⁶³ the regulations do not go very far to prevent this from happening. In proposing the new regulations, the FDA stated,

The proposed regulation has been drafted to permit any individual plaintiff who experienced an adverse event and subsequently has become involved in medical malpractice litigation with the person who reported the event to obtain all the information contained in the adverse event report. In this situation, where both parties to the litigation know each other's identities, the interests of the parties in protecting this information is minimized and, therefore, would not impose a significant disincentive to reporting.¹⁶⁴

The extent to which adverse drug event reports are confidential in other contexts remains unclear. Some states have statutory confidentiality protections that may be more protective than the FDA statute since they "protect from discovery information that is collected for quality assurance and peer review purposes."¹⁶⁵ Although the FDA regulation has a preemption provision, the language seems to preempt only those state statutes that would require disclosure, not more protective ones.

Undoubtedly there remains a perception that reporting increases physician malpractice liability because it constitutes an admission by the doctor that an adverse reaction occurred that was probably unanticipated. This is a misperception because that information, in and of itself, does not mean that the physician was negligent, which is critical in proving malpractice.¹⁶⁶ The only time a legal action can be brought against a physician with respect to the use of a drug is when an injured patient questions the doctor's medical judgment in light of standards of care generally exercised by the medical community.

An article in the SOUTHERN MEDICAL JOURNAL in 1994 explained the liability structure.¹⁶⁷ Doctors are found negligent if they contribute to an injury by falling below the standards of practice in the community.¹⁶⁸

¹⁶³ "FDA believes that if the identities of reporters or patients were made public or available to third parties, health care professionals would be much more reluctant to submit voluntary adverse event reports for fear of involving themselves and their patients in litigation." 59 Fed. Reg. at 3947, *supra* note 8.

¹⁶⁵ Witmer, *supra* note 154 at 544.

¹⁶⁶ See Mayfield, *supra* note 156, at 265 (arguing that adverse reports are not relevant to a determination of causation).

¹⁶⁷ Michele B. Kaufman, PharmD, et al., *Physicians' Liability for Adverse Drug Reactions*, 87 S. MED. J. 780, 781 (1994).

¹⁶⁸ See *id.*; A. Russell Localio, JD, MPH, MS, et al., *Identifying Adverse Events Caused by Medical Care: Degree of Physician Agreement in a Retrospective Chart Review*, 125 ANNALS INTERNAL MED. 457, 457 (1996).

This happens in two ways: by failing to do something, or by doing something incorrectly. Many factors are involved in assessing the requisite standard of care. The inquiry is into whether:

⊘

the doctor should have been aware of the risks involved in prescribing the medication

⊘

the manufacturer's literature had warnings which were not followed

⊘ a physician exercising reasonable care would have read the literature

⊘ the expected benefits of the drug justified exposing the patient to its risks

⊘ the doctor failed to perform specific tests recommended in the literature

⊘

the patient had a history of any specific drug-disease interactions or relevant experiences about which the physician should have known

⊘ the doctor should have noticed the adverse effect of the drug when it occurred and taken countermeasures

⊘

the medication could have been stopped in time to avoid injury, and

⊘ the countermeasures taken were adequate.¹⁶⁹

In general, when physicians prescribe a drug for a non-approved indication (an off-label use), they do so at

¹⁶⁹See Kaufman, *supra* note 167, at 781-82.

their own risk. This essentially means that they must be prepared show the use as being within the standard of care. Unless prior similar adverse drug reactions are published in the medical literature, they cannot be used as the basis for liability since physicians are not assumed to know this information that is not generally available to the public.¹⁷⁰

Ironically, a perspective that fears reporting due to liability concerns is in itself counterproductive. The FDA can implement informative and preventative measures to combat suspected ADRs. These measures decrease the recurrence of ADRs and therefore result in fewer malpractice lawsuits about ADRs. Consequently, reporting adverse reactions has the potential of reducing physician liability by allowing the FDA to act preventatively. Furthermore, reports document the uncertainty of the causes of some adverse reactions and the fact that they are unpreventable.¹⁷¹

The key question in assessing liability fears is what information is gained from the disclosure of ADR reports that could be useful in a plaintiff's malpractice case. If a patient has initiated a negligence case, she will already have access to her medical records, which describe how the doctor responded, if at all, to the drug event and include most of the MedWatch report information. The only potentially important information that could be gleaned from ADR reports is information pertaining to the doctor's state of mind. If the doctor failed to include in his report a preexisting medical condition or concurrent medication that may have been responsible for the event, it may be "evidence" that he had not thought of a connection prior to prescribing the medication, or that he had not read the literature on which conditions or medications cause complications with the prescribed drug. The question of whether a reaction was foreseeable and how that relates to reporting is rather complicated. If the reaction was unheard of, then the doctor could not have foreseen it and its occurrence does not indicate practice below the standard of care regardless of what was

¹⁷⁰See *id.* at 782.

¹⁷¹See Witmer, *supra* note 154, at 544.

included in the report. If the reaction was described in the literature as occurring occasionally, but did not include any conclusions about how to avoid it, its occurrence still would not seem to reflect negatively on the doctor's standard of care, unless there existed a less "risky" alternative. But, if the reaction was described in the literature with preventative measures, and the doctor failed to follow those, then reporting the reaction along with an implicit admission of not having followed those recommendations may be meaningful in arguing that the doctor acted beneath the standard of care. The very existence of the adverse drug event report and the identity of the reporter are also important to some plaintiffs. But, if the report's contents are not legally relevant, it is unclear why its existence should have much significance.

Therefore, in sum, since the only new information found in adverse event reports is about the doctor's supposed mental state concerning the relevant medical history and concomitant medical products, the risk to the doctor is in the overall implication that submitting a report establishes that a reaction was unforeseen and serious, when perhaps he should have anticipated it. It may be that the relevance of this information, to the extent that it is at all relevant, would be dramatically lessened if someone other than the treating physician completes and files the report form. In such a case, it would be less probative of the physician's thoughts when he prescribed the medication.

3.

Avoiding disclosure of reports

Among the methods of dealing with this liability issue, the force of which may be increasing as damage awards

increase, are attempts at decreasing the impact of ADR reports in court. In her paper entitled *Preventing manufacturer compelled disclosure of confidential information contained in voluntarily submitted adverse event reports*, Bonnie L. Mayfield explains how defense attorneys can attempt to exclude the admission of these reports from evidence, once they have been discovered.¹⁷² These exclusions apply both to the patient's individual adverse event report and to compilations of other similar adverse event reports. Initially, one can argue that adverse event reports are irrelevant since they do not prove causation, particularly because of the inherent uncertainty in the relationship between the drug and the reaction.¹⁷³ Furthermore, they lack probative value since they are not verified for accuracy. The inclusion of multiple adverse event reports is also not useful in proving causation because, as explained previously, a compilation of reports cannot be used to determine the frequency of reactions and should not be used for epidemiological purposes. Also, adverse event reports are not comparable for causation purposes unless they are substantially similar and arose from the "same cause" which is extremely difficult to determine and prove.¹⁷⁴ Mayfield also argues that even if these reports were remotely probative, allowing voluminous packages of adverse event reports into evidence would violate Federal Rule of Evidence 403 since it would prejudice, confuse and mislead the jury.¹⁷⁵ Finally, Mayfield explains that these reports should be excluded as inadmissible hearsay under Federal Rule of Evidence 802 since they are being offered for the truth of the matter asserted but contain statements by others, and they do not fall into any of the exceptions.¹⁷⁶ Furthermore, often the reports contain multiple layers of hearsay.¹⁷⁷ While most of these arguments apply equally to the plaintiff's individual ADE report and general ADE reports that the plaintiff might seek to admit into evidence, the hearsay argument is probably much less potent when discussing the adverse event report in the actual case because the reported

¹⁷²Mayfield, *supra* note 156, at 277-84.

¹⁷³*Id.* at 278.

¹⁷⁴*Id.* at 279-80.

¹⁷⁵*Id.* at 281.

¹⁷⁶*Id.* at 283.

¹⁷⁷*Id.*

information is arguably state of mind evidence and would not be offered for its truth. In addition, these arguments pertain to the admission of ADE reports even if in a particular case the plaintiff's doctor did not file one. Therefore, if successful, these arguments would mean that a reporting physician would not have to worry about increasing the possibility of his own personal liability or that of physicians generally by filing a report.

The arguments for exclusion on the basis of irrelevance, undue prejudice and hearsay may be valuable for defendants in malpractice litigation, but until there is some pattern of their success, the risk of ADE reports coming in as evidence against doctors may still stifle reporting. A rule that these reports are either inadmissible or undiscoverable, as discussed in the next section, may be necessary to overcome this hurdle.

4.

Potential improvements of the law

Most would agree, as Mayfield argued, that ADEs have little value in malpractice cases. A legitimate malpractice case should be able to establish causation through expert testimony. Much of the relevant information, about whether the doctor incorrectly prescribed a drug in contravention of a stated warning will already be in the patient's medical file. Moreover, such a report's inclusion into evidence would be very prejudicial because it may be hard for the defendant to explain to the jury why it is not an admission of guilt. In addition, as previously explained, the probative value is not very high. Finally, if underreporting really is significantly related to fears of litigation, the value of increased reporting may outweigh the costs of excluding this evidence. The purported harms caused by the medical profession's aversion to liability is

probably not worth the minimal, if at all, benefit from discovering and admitting ADE reports.

a.

Making ADEs inadmissible or undiscoverable

One option for dealing with the liability cause of underreporting would be a statute, regulation, or case providing that adverse event reports and their existence in a given situation are inadmissible in a malpractice action. Reports, then, could not be introduced into evidence and the very fact that an event was reported to the FDA or a manufacturer could not be presented at a trial. In the comments to rule §20.63, the FDA rejected a recommendation to prohibit adverse event reports from being admissible into evidence unless the reporter knew it contained false information. The reason for rejection was not exactly clear.¹⁷⁸

Congress actually passed heightened disclosure protections prohibiting admissibility of adverse event reports for medical devices. Section 519(b)(3) of 21 U.S.C. 360i(b)(3) provides that “[n]o report made under [the device user facility requirements] by a physician who is not required to make such a report, shall be admissible into evidence or otherwise used in any action involving private parties unless the facility, individual, or physician who made the report had knowledge of the falsity of the information contained in the report.”¹⁷⁹ In discussing this provision in the Federal Register, the Food and Drug Administration stated, “Congress enacted this provision to encourage private physicians to notify FDA or the manufacturer of device problems (H. Rept. 808, 101st Cong., 2d sess. 21 (1990)). This provision, however, may not be sufficient to prevent

¹⁷⁸ *Protecting the Identities of Reporters of Adverse Events and Patients; Preemption of Disclosure Rules*, 60 Fed. Reg. 16962, 16964 (1995).

¹⁷⁹ See 59 Fed. Reg. at 3946, *supra* note 8.

manufacturers from being compelled to release the reporters' or patients' identities pursuant to a discovery order."¹⁸⁰ It is remarkable that the FDA chose not to apply the same line of reasoning in their decision not to prevent the admission of adverse *drug* event reports at trials.

Another option could be to extend the confidentiality protections to prohibit discovery of ADEs altogether, not just their admission into evidence. This may reduce frivolous suits by plaintiffs who believe that adverse drug event reports imply malpractice. Such a prohibition would increase physician confidence in reporting if they did not think that the "fruits" of their report could be used against them in any way, for instance, as a key into further discovery angles. However, this may be too dramatic a move against plaintiffs, who, after all, seem to have some inherent right to know what has been reported about them. Additionally, this would probably be a much more politically bold move than just preventing admissibility, and one that would seem extremely anti-plaintiff. Ironically, if the purpose is really to enhance reporting, it is exactly the potential plaintiffs, the patients, who are the beneficiaries.

b.

Immunizing reporters from malpractice liability

It would be possible to immunize physicians who report adverse drug events from medical liability, although a cost benefit analysis may exclude this as an option. Under such a regime, those reactions that could be foreseen with reasonable care would be immunized along with the unforeseeable cases, which would not be

¹⁸⁰ *Id.*

successful in court regardless. The real question is whether it would be worth immunizing those cases of below standard of care treatment in order to dissolve misperceptions about liability, on the assumption that everyone would report everything in order to avoid liability.¹⁸¹ Not only would this waste time, but the long-term effects of this immunity may be very serious. It certainly reduces the doctor's need to stay informed about effects of medications, somewhat defeating the purpose of the quick acquisition of ADR information. This is not to suggest bad faith or laziness on the part of anyone, simply a natural shift in priorities. Given alternative means for dissolving liability fears, immunization for reporters should not be implemented.

5.

A note on selectivity and liability

Ironically, liability concerns may, in fact, increase the “selectivity” of reporting. Medical professionals may be more likely to report reactions not contained in product labeling than those covered in the labeling because the former are more “unforeseeable”¹⁸² and therefore more selective by MedWatch standards. Doctors may feel that reporting reactions mentioned in the drug labeling, by indicating that it may have been serious and *unexpected*, may expose them to liability for not having read the warnings.

¹⁸¹ Although one could imagine that physicians might want to avoid a written record of negligence.

¹⁸² See Shader, *supra* note 38, at 303.

F.

The desire to publish interferes with reporting

1.

The evidence

In 1996 a letter to the BRITISH JOURNAL OF CLINICAL PHARMACOLOGY, W.H.W. Inman, who oversaw the creation of the British Yellow Card spontaneous reporting system thirty years earlier, emphasized a preference in the medical community to publish adverse reactions rather than to report them.¹⁸³ He said that a majority of adverse reactions reported in the medical journals are not reported to the CSM. This “includes many of the best-documented and most reliable reports.”¹⁸⁴ This creates a delay between discovering the problem and dealing with it. The agency can have the product pulled off the market before the study is published. A response to his letter argued that most physicians are not influenced by this reason when deciding not to report.¹⁸⁵ The compiled studies also somewhat de-emphasize this concern. In the Italian study only 2.9% of the survey respondents admitted to having reported adverse drug reactions to a scientific journal.¹⁸⁶ It is unclear whether this was in addition to reporting elsewhere, but it is noteworthy

¹⁸³Inman, *supra* note 33, at 434.

¹⁸⁴*Id.* Professor Inman wrote,

The yellow card system failed to signal the most serious problem since thalidomide – the oculomucocutaneous syndrome caused by practolol. It was eventually revealed as a result of the publication of several series of cases that must have taken some considerable time to accumulate. Although some authors sent drafts of their papers to the CSM shortly before publication, the individual cases that were included in these papers were not reported as early as they could have been. Similar delays in recognition of problems by the CSM have occurred on several other occasions with other drugs.

Id.

¹⁸⁵Karen J. Belton et al., *Reply: Attitudes to adverse drug reaction reporting*, 41 BRIT. J. CLINICAL PHARMACOLOGY, 435, 435 (1996).

¹⁸⁶Cosentino, *supra* note 55, at 86.

even so. Unfortunately no survey directly solicited data on how many respondents had previously reported a particular adverse reaction to a journal but not to a spontaneous reporting system. The European Union study requested that respondents agree or disagree as to whether various factors influence reporting. Publishing prospects were considered important in discouraging reporting by at most 4% of the respondents (Italy), and virtually none in Portugal, Spain and Sweden. Nonetheless, publishing potential does create a bad incentive to delay reporting, particularly with unique or serious reactions. Those cases that are grounds for a publishable study are likely to provide exactly the relevant information that should be known about as soon as possible. The high selectivity of those cases means that even low levels of disincentive to report them should be minimized.

2.

Journal policies

Perhaps a policy requiring that in order to publish adverse reaction related articles the author must have previously reported those cases to the national spontaneous reporting system would be beneficial. A policy like this would probably have to be implemented by medical journals. It would seem contrary to first amendment principles for this to be a statutory or regulatory requirement. A pertinent question is how would this effect the publishability of these case studies. In arguing his position, Professor Inman stated, “I doubt if young doctors who need publications to advance their career would wish to share their experiences with a government agency. I believe this is an important reason for the relative scarcity of reports from hospitals to which most of the more serious adverse reactions must be referred.”¹⁸⁷ Yet it would seem

¹⁸⁷Inman, *supra* note 33, at 434.

that the effect of disclosing this information to a government agency would not be so defeating to publishing aspirations. The Uniform Requirements for Manuscripts Submitted to Biomedical Journals' section on Issues to Consider Before Submitting a Manuscript states,

Preliminary reporting to public media, governmental agencies, or manufacturers, of scientific information described in a paper or a letter to the editor that has been accepted but not yet published violates the policies of many journals. *Such reporting may be warranted when the paper or letter describes major therapeutic advances or public health hazards such as serious adverse effects of drugs, vaccines, other biological products, or medicinal devices, or reportable diseases. This reporting should not jeopardize publication, but should be discussed with and agreed upon by the editor in advance.*¹⁸⁸

The NEW ENGLAND JOURNAL OF MEDICINE's Editorial Policy states that

[W]e defer to the judgment of public health authorities, such as the National Institutes of Health or Centers for Disease Control, about whether prepublication release of research conclusions is warranted because of immediate implications for the public health. If these agencies make such a decision, presumably after appropriate review, we will consider a manuscript even though the results have already been released – say, in a press conference, a special alert, or the Morbidity and Mortality Weekly Report...¹⁸⁹

Also, reporting adverse events will not always result in an immediate announcement from the FDA on the drug's safety. Even if in the time between reporting and acceptance of the article for publication the FDA issues a new warning for a medication, this does not eviscerate the value of a scientific article on precisely why there is a problem and how to deal with it. To the extent that any FDA action will substantially diminish the value of an article it would have to be both quick and significant, the combination of which suggests that the ADR is one where public health would be most affected by waiting to disclose it. At some point the primary duty of doctors and medical journals is to the patients. Perhaps medical journals should set the standard with a reporting requirement and remind doctors of this obligation where it can be most beneficial.

G.

Patient involvement in reporting

1.

Medical health practitioners do not hear about many adverse reactions due to a doctor-patient information gap

There is undoubtedly a gap between patients and physicians that further limits the reporting of adverse reactions. One article highlighted the fact that all promotional material about spontaneous reporting systems targets medical practitioners and the pharmaceutical industry.¹⁹⁰ However, doctors only learn about adverse reaction occurrences from their patients,¹⁹¹ so often doctors will not find out about the problems. For instance, when the patient sees different doctors for the prescription and reaction, the patient may be the only one who makes the connection.

There are many reasons for why patients may not report adverse events. They often do not report because they are afraid to question their physicians or suggest that the doctor had erred.¹⁹² The FDA has emphasized that patients should report directly to the FDA in cases where they are embarrassed or have other reasons for not wanting to report a problem through a health professional.¹⁹³ However, it is likely that most

¹⁹⁰Edlavitch, *supra* note 85, at 1501.

It is interesting that in only one article that I read did it mention that the FDA *encourages* anyone aware of a serious adverse reaction, *including consumers*, to file a MedWatch report. See John Henkel, *MedWatch: FDA's 'Heads up' on medical product safety*, 32 FDA CONSUMER 10, 12 (1998).

¹⁹¹See Edlavitch, *supra* note 85, at 1501.

¹⁹²See *id.*

¹⁹³See Henkel, *supra* note 190, at 12.

consumers are not aware that a reporting program even exists. Therefore, reporting probably occurs most often when patients seek medical attention for their reactions and the patient or treating physician attributes the problem to the drug. One might argue that this comports with FDA's goal of only reporting serious events. Still it would be preferable for a medical practitioner to hear about each adverse event and decide whether it is "reportable" than to never learn about it. Even if the FDA only wants serious events reported, the information may also be important to the doctor for therapeutic reasons.

2.

The FDA does not often hear from patients although direct patient reporting can be beneficial

The American MedWatch system currently accepts patient-submitted reports, but that is not highly publicized. Patients are invited to report adverse events using the same forms as health care professionals. A study comparing pre- and post-MedWatch reporting showed that although the percentage of reports from pharmacists increased and the percentage of reports from physicians decreased, the percentage from non-health care professionals stayed static at 6%.¹⁹⁴ It is interesting that the percentage of consumer reports did not change. Given that the MedWatch advertising campaign did not target consumers,¹⁹⁵ and MedWatch increased the total number of reports, the fact that the percentage of patient reports stayed static indicates that the number of their reports also increased after MedWatch. Presumably those patients who are medically informed were influenced by MedWatch's advertising efforts. Still, patients generally are an untapped resource for adverse event information.

¹⁹⁴Piazza-Hepp, *supra* note 47, at 1437-38.

¹⁹⁵See Edlavitch, *supra* note 85, at 1501 (pointing out that promotional material about spontaneous reporting systems targets the medical and pharmaceutical communities almost exclusively).

There is reason to believe that involving patients in reporting yields a different set of adverse event data. A Dutch study performed in 1999 compared information gained from spontaneous reporting and information gained from daily ward visits of patients.¹⁹⁶ During the ward visits an investigator asked the patients about whether they had possibly experienced any adverse drug events.¹⁹⁷ The ward data was compared to adverse drug event data on the same population collected by spontaneous reporting from doctors and nurses. The study revealed that the doctors reported a significantly larger number of serious and unknown ADEs than the patients did during the ward visits.¹⁹⁸ Nurses and patients had statistically similar reporting data.¹⁹⁹ Interestingly, however, only patients, not doctors or nurses, reported adverse drug events from new drugs.²⁰⁰ The study concluded that as a result of the split between doctors being the main reporters of serious and unknown ADEs in hospitalized patients, and patient interviews yielding more ADEs of new drugs, it may be cost effective to do daily ward visits for patients using new medications.²⁰¹ Although the cost of daily ward visits would probably be extremely high, this evidence suggests that it may be particularly useful to encourage patients to report suspected reactions to their doctors or the FDA, since their information may be substantively different from the information that doctors alone usually provide.

¹⁹⁶P.M.L.A. van den Bemt, et al, *Adverse Drug Events in Hospitalized Patients*, 55 EUR. J. CLINICAL PHARMACOLOGY 155 (1999).

¹⁹⁷*Id.* at 156.

¹⁹⁸*Id.* at 155.

¹⁹⁹*Id.*

²⁰⁰*Id.*

²⁰¹*Id.*

3.

Mechanisms for encouraging patient reporting to doctors or to the FDA directly

This doctor-patient gap alone may be a reason to target patients with advertising, as is done for medical professionals, to encourage them to report troubling drug reactions either to their physicians or pharmacists, or directly to the spontaneous reporting system.²⁰² In order to have an efficient system, we need to educate patients in identifying and reporting adverse reactions that may be drug related. The FDA is taking steps to increase access to patients and involve them in the process by partnering with pharmacy chains, which are another avenue to patients and their reactions.²⁰³ Among the improvements to the pre-MedWatch reporting system recommended by Stanley A. Edlavitch, Ph.D, in *Adverse Drug Event Reporting, Improving the Low US Reporting Rates*, was sending a clear message for medical and *lay* communities on what and how to report.²⁰⁴ Additionally he wrote that “[p]racticing physicians, pharmacists, other medical practitioners, and the general public should be familiar with the system, encouraged to appropriately report suspect events, and be assured the system is operating optimally to protect health.”²⁰⁵ While MedWatch has improved medical professionals’ knowledge of spontaneous reporting, this was only one link in the chain. The lay community still lacks this critical knowledge.

a.

Encouraging reporting to medical professionals

Encouraging patients to report reactions to their doctors may significantly improve awareness of reporting

²⁰² See Edlavitch, *supra* note 85, at 1501.

²⁰³ See Henkel, *supra* note 190, at 15.

²⁰⁴ Edlavitch, *supra* note 85, at 1501.

²⁰⁵ *Id.* at 1502.

programs, enhance their effectiveness, and benefit patient treatments. A British study published in 1988 monitored the feasibility and benefits of patient encouragement.²⁰⁶ Patients who were prescribed a black triangle drug were given a leaflet by the pharmacist encouraging them to report any adverse reaction to their doctor. Reports to doctors of adverse reactions rose from 10 out of 1000 to 23 out of 1000. “The odds of an adverse reaction being reported to the doctor were increased by a factor of 2.2 for patients given a leaflet.”²⁰⁷ It is noteworthy that the study concluded that this increase was not statistically significant at the 5% level.²⁰⁸ Despite all this encouragement, however, only one “yellow card” was submitted to the CSM. Also, one patient out of the total 1057 was so alarmed by the leaflet advice that the patient refused to take the medication. This was the only reported negative comment by a patient.²⁰⁹ Otherwise, the method was well received by the patients, doctors and pharmacists involved in the study.²¹⁰ The authors ultimately concluded that the results suggested that patients can be stimulated to report adverse reactions to their doctor, but that any potential benefit is lost if these reports are not relayed to the Committee on Safety of Medicines by the doctor.²¹¹

b.

Encouraging reporting to the FDA directly

Simply listing the MedWatch (or other spontaneous reporting system) web address on medication bottles would probably significantly increase the number of direct patient reports. If nothing else, it would inform

²⁰⁶J.P.M. Campbell, MD, MRCP & J.G.R. Howie, MD, FRCGP, *Involving the Patient in Reporting Adverse Drug Reactions*, 38 J. ROYAL C. GEN. PRAC. 370 (1988).

²⁰⁷*Id.* at 370.

²⁰⁸*Id.*

²⁰⁹*Id.* at 370.

²¹⁰*Id.* at 371.

²¹¹*Id.*

patients of spontaneous reporting systems in general, which may increase communication with their physicians; at the very least, the curiosity of many would be whetted, and they would visit the site. It is also possible that a certain patient groups would particularly benefit from this information. Teenagers, for example, whose adverse reactions are very hard to monitor because of their desire for independence with respect to their medications,²¹² are also among the most web-connected age groups. They may be likely to take advantage of Internet reporting options if they are aware of them, particularly because of the comparable impersonality as compared to discussing problems with their doctors.

There are some serious limitations with a publicized direct patient reporting system. One concern about patient reporting is the quality of reports. A larger quantity of reporting is useful only if the reports are of good quality and include all the relevant information.²¹³ This may explain a reluctance to partake in concerted efforts to increase patient reporting.²¹⁴ There is no easy way to deal with this problem, but one possibility is to have a telephone line for hospital patients to report to hospital pharmacies.²¹⁵ The possibility of human interaction would allow trained professionals to seek the relevant information. Alternatively, encouraging patients to report ADEs to the FDA by telephone would have similar benefits. However, having representatives available to solicit more detailed information from patients would entail increased administrative costs. A second concern with patient reporting is that there may be no way to prevent an individual from sending or calling in false or multiple reports so as to skew the data. This may not be easily prevented without involving an intermediate person who can attempt to serve as a filter. Since doctors can serve as the intermediaries, it may be preferable to encourage reporting to them instead of directly to the FDA, especially since doctors already have therapeutic reasons for desiring this information.

²¹² See Nightingale & Hoffman, *ADOLESCENT HEALTH* at 279, *supra* note 10.

²¹³ *Cf.* van den Bemt, *supra* note 196, at 156.

²¹⁴ See generally Andrew S. Mitchell, et al, *Patients as a direct source of information on adverse drug reactions*, 297 *BRIT. MED. J.* 891 (1988).

²¹⁵ See van den Bemt, *supra* note 196, at 158.

c.

Conclusions on patient involvement efforts

Since direct pharmaceutical advertising has taken over our televisions, one of the biggest concerns has been the affect this has had on medical treatments. Doctors are being pushed by their patients to prescribe the latest medications. If it is true that patients take such an interest in their treatments so as to “force” doctors to listen to their requests, it is hard to believe that they would not be amenable to at least some involvement in adverse reaction reporting. Of course, a reaction report will not necessarily decrease their pain, which may create the incentive to request specific medications in the first place. Still, would patients informed about MedWatch be more inclined to tell their doctors about adverse reactions that they had? Would they be more inclined to ask or even push their doctors to report adverse reactions? In a world where everyone wants to share their personal traumas with society and have society respond,²¹⁶ involving patients may be the best approach to encouraging physician reporting. Advertising MedWatch directly to consumers may seem bizarre (although maybe not ineffective) if it took the form of a television add. But to correspond with the product labeling point, what if product labels included the statement: “STOP USE AND CONSULT A DOCTOR IF...XXX...OR OTHER ALLERGIC REACTION DEVELOPS. ENCOURAGE YOUR DOCTOR TO REPORT THIS INCIDENT TO THE FOOD AND DRUG ADMINISTRATION IN ORDER TO HELP PREVENT SIMILAR REACTIONS IN THE FUTURE. SEE <http://www.fda.gov/medwatch/index.html> FOR MORE INFORMATION.”? It may seem idealistic that anyone would either read this warning or follow its instructions, but it is not clear that citizens are so apathetic to the causes of humanity that such a plea would be wasted. If we are quick to tell each other which restaurant gave us food poisoning, we may feel equally compelled in this instance.

²¹⁶See, e.g., THE OPRAH WINFREY SHOW, THE JERRY SPRINGER SHOW & THE REAL WORLD.

Product labels printed with the MedWatch reporting website as well as a word encouraging patients to report problems to their physicians may be an ideal mix of information and encouragement.

Conclusion

While the Food and Drug Administration's spontaneous reporting system has significantly improved reporting rates in the United States, there may be some ways of further enhancing adverse drug reaction information in the United States and worldwide. Depending on their costs, these extra efforts may be worthwhile if they can significantly reduce the amount of time between a product's availability on the market and the discovery of its harmful effects. Studies worldwide have provided useful information as to why spontaneous reporting systems do not receive more cases from the medical community. This piece has included the proposal and discussion of several possible improvements to enhance current reporting quality and rates. Although some important improvements may involve modifications to the reporting system or informing the patient community, part of the answer to resolving reporting problems is not within the direct control of the FDA because part of the problem involves the current health care structure and inconsistencies in the goals of adverse reaction reporting and the legal system. Therefore, while some improvements require more confined efforts, others may have to deal comprehensively with larger institutions.

Appendix A

Table 1: Compilation of Answers from Certain Questions in Attitudinal Studies

Question	European Union										Italy	Ireland			The Netherlands			
	Den.	Fr.	Ire.	Ita.	Hol.	Por.												
National Reporting Rate: reports/10 ⁶⁶ population	390	319	44	76	9	121	347	340										
Ever diagnosed an ADR											77				98			
Ever reported an ADR	67	74	53	19	33	49	44	65	63	50*	70	74	50	62	64	68	38	
	GP	85	77	60	28		52	50	59	77	77							
	Spec.	61	71	51														
Reported to the pharmaceutical manufacturer	52	39	16		17	43	5	16	17	44		47	33	41	34	55	31	

Reported to the health authority	55	39																
Encountered ADRs which they did not report at all											90				86	81	72	
Do not know how to report to the national health authority	3	20	22	38	13	31	11	9	3	30*	23	23	23		20	22	37	
Do not know of the need to report ADRs																		

Why report?																			
Unusualness of the reaction	63	64	82	73	77	64	70	85	89	37									97*
Involved a new drug	83	64	86	74	76	75	85												
Severity of the reaction	88	88	95	91	93	99	93	84											
Why Not report?																			
Unaware of a national reporting system																			
Apathy or indifference																			

Uncertain the drug caused the rxn. (EU, IR, NE)/ Mul- ti- ple drugs make it un- clear (SA, UK)**	52	51	68	34	29	76	44	49		73	73	74		78	66
The re- ac- tion was clin- i- cally neg- li- gi- ble, triv- ial															

Aware of similar rxns. (IT) / Too well known to report (IR, NE)								
Unavailability of the report form	8	N/A	52	55	25	64	23	21
Uncertain of what to report (IT)								
Assume marketed drugs are safe	2	1	11	5	9	26	11	4
SRS's are not valuable								
<i>Question</i>	<i>European Union</i>	<i>Italy</i>	<i>Ireland</i>	<i>The Netherlands</i>	<i>The Northern</i>	<i>South Africa</i>		
	Den.							

Reporting is too bureaucratic or takes too much time								
Drug wasn't new								
Too busy to report								
Fear of legal liability	0	1	4		5		2	11
Should get reimbursed								
Want to publish the cases	<1	2	1	4		2	0	0

All numbers are percentages unless otherwise specified, and they have been rounded to the nearest whole number.

The countries in the European Union study were: Denmark, France, Ireland, Italy, Holland, Portugal, Spain,

Sweden and the United Kingdom

Symbols and Abbreviations:

EU: European Union

IR: Ireland

IT: Italy

NE: The Netherlands

NP: Not provided

SA: South Africa

SRS: Spontaneous reporting system

UK: Northern United Kingdom

* Converted from the data provided in the study

** There seems to be a distinction between these two questions. The category “uncertain the drug caused the reaction” seems to entirely encompass the category “multiple drugs made it unclear” but also includes other uncertainties.

† This data came from fill-in questions and not multiple choice or yes/no questions. The numbers provided without the symbol came from multiple choice or yes/no questions. Sometimes both fill-in and select an answer questions were posed soliciting similar information in the same study. It may not be accurate to compare the responses to the two different kinds of questions because of a memory-triggering effect created by the multiple choice and yes/no questions. Although a participant may have agreed to a question, she may not have thought to include that point in her fill-in answer.

Appendix B

<http://www.fda.gov/medwatch/safety/3500.pdf>