The Practicing Clinician and Regulatory Safety Concerns

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Abstract: Pharmaceutical agents are prescribed to produce a therapeutic effect, but safety concerns require constant attention to the benefit:risk relationship inherent in their use and the needs of the individual patient. Such calculations involve assumptions about the likely tolerability of harm, in that greater safety risks may be acceptable for use of a life-saving drug, compared with those acceptable for an agent providing only improved "quality of life." Making such assumptions is an activity integral to the bedside clinician's role, is done during many (perhaps most) patient encounters, and is often undertaken with inadequate information. The historical mandates for regulatory agencies, such as the Food and Drug Administration (FDA) in the United States, have evolved over the past decades to include an intense focus on drug safety. Communicating information about medicinal risk remains a major responsibility for the FDA and similar bodies, but the initiatives undertaken have had variable, and often limited, effectiveness in penetrating the physician-patient interaction. Barriers to the successful communication of safety-related issues include the myriad of influences on and within the FDA, the time constraints on physicians involved in clinical practice, and the methodologies used to share information about both established and new drugs. Current efforts to assess the effectiveness of regulatory efforts at risk communications should lead to changes in the approaches used and, ultimately, improvement in the safe use of both new and established drugs.

Keywords: Communication, FDA, pharmacovigilance, REMS, risk:benefit, safety.

INTRODUCTION

"Drug safety" is a broad topic, ranging from assumptions of human toxicity derived from *in vitro* laboratory procedures to post-marketing pharmacovigilance surveys conducted to detect "safety signals" [1]. The purpose of this review is to examine the efforts by the United States Food and Drug Administration (FDA) to inform clinicians about known, serious and potentially life-threatening risks associated with approved drugs, i.e., "labeled risks," ideally in juxtaposition with comprehensive presentation of benefit information, and the consequences of those efforts.

The public health mandate for the FDA is to assure that drugs approved for marketing are pure, safe, and effective. *Purity* is assured through myriad regulations affecting drug manufacture, as well as periodic inspections of commercial manufacturing facilities. *Efficacy* must be demonstrated in pre-registration clinical trials, whose statistical analyses and clinical import are carefully scrutinized in the review of New Drug Applications, submitted to FDA by a drug's sponsor [1]. There is no standard measurement of *safety*, however, and it remains a nebulous concept, open to potentially broad interpretive conclusions and actions (sometimes based on a single serious safety event), when not considered within the context of the potential benefit to the patient. Individual therapeutic decisions depend largely on the joint consideration by clinician and patient regarding subjective and objective assessments of a drug's benefit: risk relation, whether the clinical benefit derived from a drug's use is greater than the risk associated with its administration, or the risk of doing naught, taking into account all matters unique to that patient, such as demographics, concurrent medications, and concomitant illnesses, which may not have been evaluated in preapproval studies. This individual decision is not universally based on a set of standard data elements, such as pharmacodynamic properties, registration trial data, or post-marketing adverse events surveillance, but rather on a host of clinical encounter factors that include variables such as a patients' trust in his or her care provider [2, 3], the available time for the clinical encounter and personal beliefs [4, 5]. Under a standard drug approval process where only a single agent has efficacy in the management of a serious disorder, even though severe, or potentially lethal, toxicity may occur, the FDA may approve the drug for marketing, and clinical use, but require the drug's sponsor to communicate with the clinical community in an attempt to educate and inform those giving the drug about known toxicities and their management. This process has evolved and is now incorporated into what is termed Risk Evaluation and Mitigation Strategies (REMS) [6].

The FDA has concentrated on efforts to communicate the risks potentially associated with a drug's use, using variations in approved product labeling [7], recommending use of Patient-Provider Agreements [8], requiring restrictions on drug distribution availability [9], and direct messaging to physicians and other healthcare providers [10], such as periodic internet safety communications. There have been few, if any, meaningful attempts to assess the validity of these regulatory interventional processes used in risk communication activities in achieving desired outcomes,

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either by the FDA or by drug manufacturers. Furthermore, there are a number of factors that may hinder effective FDA-to-physician communications: clinicians are extraordinarily busy and often do not pay attention to federal government missives (understanding that physician licensure is a matter overseen by state governmental agencies); medical journal content often has an imbalanced focus on new discoveries, procedures, and efficacy, rather than drug safety [10] (in that negative studies are not often published/submitted, though such results may be accessible *via* clinicaltrials.gov postings); and, given the rapid modification of practice standard guidelines, there is an inherent knowledge deficit upon which to rest new understandings and information [11, 12]. Further, many physicians may be concerned about a perceived imbalance in communication of possible safety issues following FDA approval (tripling of black box warnings after 2004), without concurrent new efficacy/benefit reports [13-15].

We shall examine the effectiveness of the processes and procedures used by the FDA to communicate "medicinal risk" to the clinical community, the obvious difficulties in assuring attention to and compliance with risk communications on the part of physicians, and the need for new approaches in the evaluation of current efforts in the risk-communication arena in the interest of more balanced benefit:risk determinations.

THE REGULATORY MILIEU: MANY HANDS STIR THE POT

The **Pure Food and Drug Act** of June 30, 1906, which took effect in 1907, is a US federal law that mandated the federal inspection of meat products and addressed issues with the manufacture, labeling, and use of drugs. It is generally considered to be the basis for the founding of the FDA (so named in 1930), evolving through repeated legislative steps that eventually resulted in an agency entrusted with the power to approve, or disapprove, pharmaceutical agents for marketing and sale in the United States. As a major branch of the federal government whose decisions have profound commercial as well as clinical impact, its policies and procedures are subject to a myriad of influences, often from the political sphere [16]. In addition, its review and approval processes are subject to criticism for being too anxious to bring potentially unsafe drugs into the clinical arena [17] or, at the same time, for being so focused on safety considerations that valuable therapies cannot be obtained for patient use [18]. Even the design of clinical trials considered conventional and acceptable to the agency, as well as the statistical consideration of results, have been called into question [19]. Recently, the Institute of Medicine (IOM) compiled and released two major reviews of the FDA's activities: a consideration of the approval processes for medical devices in 2011 [20] and an in-depth overview of the ethical and scientific issues involved in the FDA's approaches to drug safety in 2012 [21]. The earlier report suggested that significant changes were required in the legislative foundation for the agency's regulatory framework, and the latter proposed a major change in the FDA's approach to drug safety, moving from a primary emphasis on pre-approval clinical trial data to a lifecycle program in which drug safety would be continuously evaluated throughout the development and clinical use of pharmaceuticals. The FDA, then, exists in a maelstrom of competing influences and pressures, in which the need to communicate effectively with the bedside clinician may find a lower priority due to the requirements of federal, rather than hands-on, practicing stakeholders.

REGULATORY INITIATIVES EMPHASIZING BENEFIT:RISK

One of the seminal events in the history of drug regulation occurred with the use of thalidomide as a sedative to treat morning sickness, as well as a sleep aid, between 1957 and 1961, during which time millions of tablets were distributed to physicians in the United States for clinical testing programs. The drug was never approved by the FDA, and it was withdrawn from distribution after being found to cause birth defects, including phocomelia [22, 23]. In response, Congress passed in 1962 the "Drug Efficacy Amendment" (also known as the Kefauver-Harris Amendment) to the Food, Drug, and Cosmetics Act of 1938, requiring, among other things, that drug manufacturers provide proof of the effectiveness and safety of their drugs as a condition for FDA approval, rather than just safety alone, as had been required previously under the Food, Drug and Cosmetics Act. Since that time, there has been an ongoing emphasis on drug safety within the agency as well as Congressional mandates to continue to bolster safety surveillance [24, 25].

Under the Prescription Drug User Fee Act (PDUFA) III of 2002, provisions were included to fund more safety staff in the Center for Drug Evaluation and Research (CDER) and resulted in the development of 3 risk management guidances – among a host of others [26]. The next major event was the passage of the Food and Drug Administration Amendments Act (FDAAA) of 2007 [27]. This catch-all compilation renewed and affirmed several different legislative and regulatory initiatives, including the PDUFA, the Medical Device User Fee and Modernization Act (MDUFMA), and the Best Pharmaceuticals for Children Act (BPCA) together with the Pediatric Research Equity Act (PREA); it added emphasis on therapies for tropical diseases while requiring reporting of basic results of clinical trials of medicines and devices subject to FDA regulation on the freely accessible Internet site <http://www.clinicaltrials.gov>. Of particular importance, the user fees generated under PDUFA were anticipated to support a variety of new emphases and initiatives in the areas of drug safety, including tentative approaches to the IOM's recommendations for a longitudinal (life-cycle) approach to safety issues, such as enhanced post-marketing pharmacovigilance programs and requirements for manufacturers to compile registries and improve reporting of adverse events to the FDA. Among the safety-related provisions of the Act, the FDA was given specific authority to require.

- Manufacturers to conduct post-approval studies to assess known risks from pharmaceuticals, or to explore hypothetical risks (and for the first time the ability to enforce such requirements, using labeling revisions and civil monetary penalties as "teeth" in the FDA's enforcement toolbox);

- New safety data be added to previously approved product labeling which could independently be imposed by FDA (previously there was a more conjoint responsibility by sponsor and agency); and
- Manufacturers prepare and submit for approval a REMS for products with known or suspected adverse effects which were identified as being potentially amenable to risk management interventions, in an attempt to assure that a drug's benefit is appropriate to the risks inherent in its use. The FDA may now require a REMS for any drug, at any stage in its development or clinical use. Failure of manufacturers to comply with the FDA's REMS requirements can result in substantial financial penalties and other enforcement actions [27].

Since a REMS program must be created for each individual drug found to have serious risks associated with its appropriate use, the FDA issued a draft Guidance document in September 2009 [28] to assist manufacturers in compliance with the agency's mandates. That time the FDA did not engage practice communities in the development of such actions; therefore, the potential practicality of those plans at the pharmacy or bedside has yet to be assessed. At the present time, the FDA is seeking advice from stakeholders to update and improve the present requirements. For instance, a REMS may utilize a number of different tools and approaches, including

- A communication plan, to educate the medical community on the risks associated with a drug's use and on what is known about how to treat or mitigate such risks;
- A medication guide, materials written for patients that provide relevant information about the risk of using a specific drug, which must be provided to patients by the pharmacists involved in distribution as well as reviewed by the clinician prescribing the drug for discussion with the patient;
- Elements to Assure Safe Use (ETASU), which constitute a program or plan to assure, as best possible, the proper and safest use of a specific drug; such ETASU plans might involve restricting drug distribution to specialty pharmacies, requiring a drug to be prescribed only by specifically trained physicians, or the requirement that patients given a specific agent must be enrolled in a drug-use registry. An Implementation Plan, describing how the agreed elements will be put into effect, is generally required, as well; and
- Serial assessments of the effectiveness of mandated REMS in achieving the objectives defined by the FDA; such assessments must be generally undertaken at least at 18 months and then at 3 and 7 years after a drug is introduced to the market. The specific REMS program agreed between the manufacturer and the FDA may require revision after evaluation of its effectiveness.

As of September 25, 2012, there have been 268 REMS programs mandated, with 69 such programs currently in operation [29].

BENEFIT:RISK AT THE BEDSIDE: HOW DOES RELEVANT SAFETY INFORMATION AFFECT CLINICAL USE?

Following the IOM reports and the FDAAA legislation in 2007, both systemic and procedural changes are occurring in the FDA's considerations of the wide variety of issues subsumed under the label "drug safety". Notwithstanding these intra-agency initiatives, the gulf between the FDA and the community of clinicians providing care remains deep in regard to the information about and understanding of safety concerns for specific drugs.

Conventional approaches to information dissemination from the FDA have included safety-issue-related changes in product labeling, such as the Black Box warnings intended to alert clinicians to adverse reactions that might be severe or even fatal. Following reports of increased suicide risk in pediatric patients given antidepressant drugs in 2004, the FDA issued a Black Box warning that resulted in a 58% decrease in use of these agents in children and adolescents. In a survey sent to 2395 pediatricians, Cheung *et al.* [30] examined responses from 670 physicians (38%), reporting that 72% were aware of the warning and that 80% of those had changed their prescribing practices, with some halting use of antidepressants altogether. Contents of the Black Box, however, may differ from prescribing information available in major drug information resources widely used by physicians and pharmacists, presumably because the Black Box contains the most current data; this discordance may be a source of concern for prescribers. Cheng *et al*. found that of 59 Black Box warnings about contraindicated drug combinations, only 68% could be confirmed by a search of drug interaction databases available to the clinical community [31]. Although the most current label information is available at the National Library of Medicine's Daily Med (http://dailymed.nlm.nih.gov), site utilization is hinderedby lack of familiarity as well as deficiencies in workflow integration at the patient level.

Nonetheless, it remains the case that widespread appreciation of the risks associated with drug therapy varies among different groups, and this circumstance may impact the types and intensity of regulatory emphasis. For instance, the morbidity and mortality resulting from overuse and abuse of opioid analgesics in the United States over the past decade has been given significant attention in the professional literature [32] but is only now becoming grist for the popular press's mill [33].When such safety concerns extend beyond the healthcare community into the general population, there is more pressure on the FDA to be seen publically as responsive and addressing such issues.

The REMS programs incorporate efforts to accelerate the dissemination of essential safety-related information to clinicians. For instance, in recognition of the opioid overuse epidemic in the United States, the FDA has mandated development of a REMS plan for the class of extended-release, long-acting opioid drugs. Manufacturers of these products must provide education for physicians about appropriate use and risk potential, as well as proper patient selection, and, at the same time, develop medication guides for distribution to patients [34]. However, medication guides and similar documents have been reported to be ineffective in patient education about specific drug risks [35], and the

education initiatives for medical staff are voluntary, without requirements for certification or knowledge testing. Furthermore, as in the case of the opioid-analgesic abuse epidemic, a REMS mandate may require a sponsor to deal with changes in the benefit:risk profile for a drug (or, drugs) which have resulted from use by healthcare providers and/or patients which is clearly different from that defined in the approved product label, and such a circumstance may not be remediable with current initiatives.

One potential source of confusion for the clinical community in general is the perception that FDA approval of a new pharmaceutical automatically assures that the agent is safe for its intended application(s) over the market life of the product. This assumption may be incorrect in several disparate but conjoined ways:

- The regulatory decision that a drug has demonstrated efficacy that outweighs the safety risks observed during pre-approval testing in highly selected, carefully monitored patient populations implies only what is stated: that the demonstrated clinical benefits are judged to justify use in the targeted population studied (which often had restrictive inclusion criteria for such limitations as age, concurrent medications, and other significant clinical variables) despite whatever toxicities have been found, not that the new agent is safe and can be dispensed without appropriate oversight and care. Here, the burden is on the clinician to collate such information as might be available through published reports and approved advertising materials from drug manufacturers and to make reasonable decisions about use of new compounds in patients. Too often, such information is limited, difficult to obtain and/or assess, or biased. Furthermore, the database may be too limited to justify a clinician's conclusion that FDA approval necessarily implies safety (or more properly, an acceptable benefit/risk profile) for use in a wider patient population, or the database may be unavailable, as publication of critical results may be delayed by the sponsor for a long period after trials are completed.

- When use of new pharmaceutical agents is extended from the constricted and well-defined patient populations in which pre-approval studies are conducted to an unselected population in a clinical practice setting, toxicities that were not observed or appreciated in randomized clinical trials may become apparent. This became painfully clear during the past decade with salient examples such as cyclooxygenase (COX) 2 inhibitors [36] and rosiglitazone [37], which were shown to increase the risk of myocardial infarction and other cardiovascular events long after they had been adopted for widespread clinical use. Telithromycin, having initially received a broad set of antimicrobial indications, was stripped of many of the self-resolving indications (e.g., acute bacterial sinusitis and acute bacterial otitis media) due to imbalanced risk:benefit for specific disease states [38]. These and similar reports contributed to the IOM report that recommended a considerable revision in the FDA's approach to drug safety and adoption of a longitudinal approach to data collection and ongoing safety assessments [21]. Psaty and Furberg, reviewing the lessons learned from the appearance of cardiovascular toxicity during long-term use of COX-2 inhibitors, summarized the situation in this fashion: "The absence of evidence here is not evidence of safety [39]." The drumbeat for revisions in the FDA's approaches to assessing drug safety, at least during the pre-approval, clinical-trial phase, is clearly having some effect, as recently reported by a team from the FDA's Center for Drug Evaluation and Research [40]. However, issues relating to effective communication of drug safety risks to the clinical community remain unresolved.

- In lifecycle management of drugs, the benefit:risk profile of an agent may change radically over years, in part because of newly recognized (unanticipated) adverse events, but also relating to the fact that safety data collection following approval of an agent is often mandatory, but benefit is rarely monitored concurrently. Hence the balance becomes skewed, and a single safety event may trigger an immediate safety label change (and/or published safety warning), while the addition of a new indication for clinical use to a product label usually requires years to complete.

- The depiction of benefit:risk relationships may be in part dependent on the degree of background information available about a given disease state under study, and the related guidelines established by the FDA for validated endpoints and similar determinations. This issue is best illustrated by comparing the likely benefit:risk profile of a candidate drug intended for use in a common (prevalent) condition for which well-established outcome measures are validated and there exist precedential approvals that serve as reference points for subsequent developers. This is in sharp contrast to a profile for a rare disease for which no trial guidance exists, where no therapy (and thus no precedent) is available and which does not have validated endpoints (often due to the scarcity of patients available for study). In such circumstances, a better understanding of unmet needs in juxtaposition to risk tolerance may require further exploration as an alternative to more traditional benefit:risk integration.

The REMS initiative includes a mandate to evaluate the effectiveness of such programs to inform or educate patients and health care providers (prescribers and/or pharmacists) about the risks associated with a drug, to which end the FDA has conducted workshops and reports on REMS evaluations [41]. In terms of connections with clinicians, the agency has focused largely on written and email communications. While this conventional approach might appear most convenient for the regulators, data are appearing that suggest it is often ineffective. Mazor *et al.* reported that "Dear Doctor letters", which are correspondence letters to health-care providers intended to communicate safety-related information, often have significant deficiencies. When rated by a panel of physicians, 25% of the letters were identified as being deficient in clarity, 36% were deficient in key information being easily discernible, and 28% were reported as being

ineffectivein communication, among other categories [42]. Importantly, such FDA communications seem more effective at simply discouraging use of targeted drugs, rather than improving the quality and safety of prescription drug use [43].

A study recently completed by Medscape evaluated use of a brief continuing medical education (CME) activity as a way to improve clinicians' understanding of the toxicity associated with use of ipilimumab, an oncolytic agent used in the management of metastatic melanoma [44]. We found that development and deployment by email of a safety communication was enhanced through the development of a CME-certified activity that reflected the FDA "Dear Doctor" letter. An analysis of answers to pre- and post-test questions showed that participation in the CME activity resulted in an increase in correct responses of 47%, suggesting an improvement of understanding and appreciation of the toxicity associated with ipilimumab use, and its management, in about half of the participants. Standard communications do not permit assessment of knowledge acquisition, and the use of email and website-based education information is rapid and cost-effective when compared to other approaches.

The daily demands on clinicians' time must severely curtail the interest in, and, therefore, the likelihood of, attention to notices from regulatory agencies, whether in print or sent by email. Abbo *et al*. have reported data from 46,431 adult primary-care visits, collected over a 7 year period by the National Ambulatory Medical Care Survey (NAMCS) [45]. The mean duration of patient contact increased over the measurement interval from 18.0 to 21.9 minutes, while the number of clinical issues addressed per visit increased from 5.4 to 7.1, resulting in a decrease in the time per clinical item from 4.4 to 3.8 minutes. Older patients (i.e., >65 years of age) had significantly more clinical items per visit, and less available time per item, compared to younger patients (P<0.001). The NAMCS data are currently available through 2009, and the trend only continues (Fig. **1**).

To put these findings into context, Yarnall *et al*. used a simulation study to point out that if the clinician were to attempt to provide all the recommended preventive services

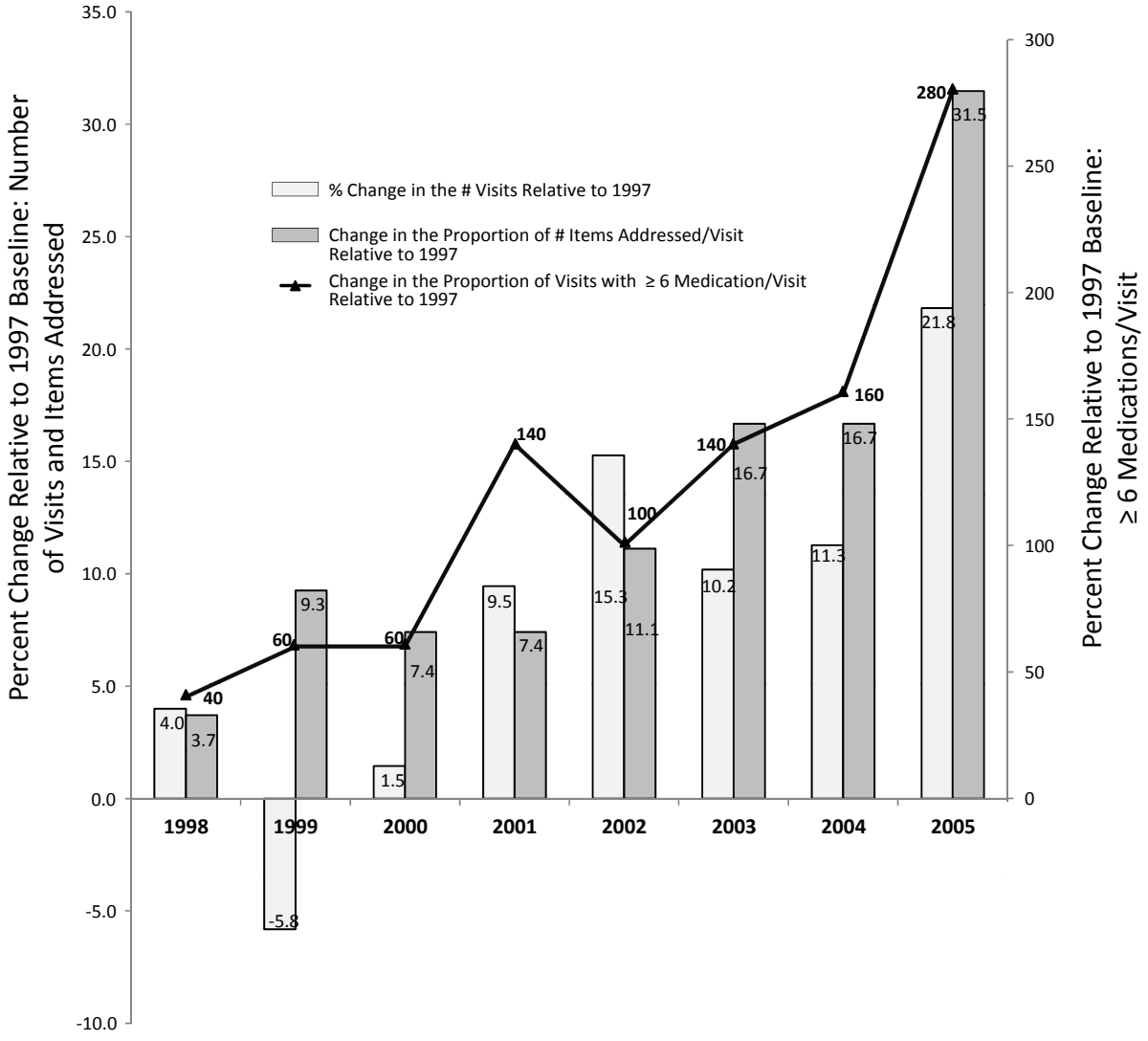

Fig. (1). Increasing complexity of the primary care clinical encounter relative to 1997 measures, from the National Ambulatory Medical Care Survey. Number of visits in millions (adapted from Abbo *et al*., *J Gen Intern Med*, 2008).

at a patient visit, such an effort would exceed the usual time allotted (7.4 hours per day would need to be allocated for preventive services alone) [46].

With primary-care physicians typically working 50 to 60 hours per week [47], finding time to acknowledge and incorporate alerts from regulatory agencies (or for other administrative tasks or information updates) is challenging. Baron reported on data abstracted from an electronic health record system used by a 5-physician practice in Philadelphia, finding that the daily activities by each physician involved an average of 18.1 patient visits, 23.7 telephone calls, 12.1 prescription refills, 19.5 laboratory and 11.1 imaging reports to review, and 11.9 consultation reports to consider [47]. Additional, more routine tasks were managed by 13 non-physician office staff employees. In a study involving direct observation of 33 internists during a typical office day, Chen *et al*. [48] reported a similar duration of time spent on patient visits and noted that about 20% of the work day was spent on patient-care activities outside of office visits. The physicians pointed out that many of the activities undertaken actually substituted for office visits, yielding a median potential savings of 5 visits per physician day. Although many of the time-efficiency studies of physician:patient interactions are primarily concerned with the costs involved in health-care delivery, all emphasize the enormous demands on clinicians' time, both in the examining room and attending to administrative tasks.

In the presence of such clinical demands, even in the most efficient practice settings it would seem obvious that dramatic changes in the nature and format of drug-safety communications will be necessary to command attention from a medical community overburdened by patients' needs.

LOOKING FORWARD

While we have sought to focus on efforts by regulatory groups to communicate drug-safety concerns effectively to those responsible for patient care, we recognize that the professional staff of the FDA (and, undoubtedly, in similar agencies elsewhere) have to deal with legislative and political influences, commercial entities anxious to accelerate approval of their compounds, a variety of professional organizations involved in health-care delivery anxious to participate in policy decisions, and, finally, the practicing clinician. In the final analysis, the clinician may be the most important but least appreciated constituency. While systemic changes are taking place in the processes involved in the evaluation and assessment of drug safety issues (e.g., the IOM recommendation for every drug product in the United States to have a benefit:risk management plan (BRMP) for continuous review [21]), wherever occurring over the life-cycle of a pharmaceutical product, attention must also be directed to the development of meaningful and productive approaches to communication of such important information to those who need it most, as well as supporting their ability to learn, integrate and apply such information. Current efforts seem to have been found wanting, and we join with Qato and Alexander in calling for "innovative methods of risk communication and mitigation" as well as "better evaluation of the effectiveness of these methods for improving drug safety and public health" [49].

The information burden on primary care clinician is substantial and growing. The complexity of patient encounters managed by US clinicians is also increasing, as evidenced by a 5-fold increase in the proportion of patient visits involving six or more medications prescribed, as well as a 2-fold increase in visits requiring oversight of three or more chronic conditions [45]. The limited time available as well as the increasing demands upon such time highlight the need to translate efforts made by non-caregiving stakeholders regarding the assessment of pharmaceutical benefit:risk at the patient level. Most efforts by regulatory authorities worldwide focus on the risk side of the equation and do not provide practical tools or information directly relevant to the practice of medicine. As discussed above, the impact of FDA tools such as Black Box warnings, Dear Doctor letters, and REMS programs do not suggest that a sustainable, scalable solution for safe use practice has been found. Furthermore, highly toxic interventions may have substantially different values of benefit:risk, based on the indication. There is a need for clinicians to rank benefit:risk based on whether the intent of treatment is to be life-saving, life-altering, or lifestyle-impacting, with marked variation in harm tolerability in each instance. Drug labeling and other communications to healthcare providers focus mainly on toxicity concerns, making such ranking more challenging due to the lack of benefit:risk focus on particular indications with potential deleterious effects on treatment administration and/or access.

Though Malcolm Gladwell has defined "tipping points" as occurring when a new trend becomes mainstream, we may be reaching a "tripping point", where new safety information is so frequent, and so amplified by media and other information sources, that a truly balanced benefit:risk depiction for clinicians to understand and/or convey has become impossible to obtain. Practitioners are faced with the continuing need for deciding how not to "trip" on the overabundance of safety information or simply how best to communicate and share such information with their patients during the brief time allotted to the clinical interaction. Of interest, the FDA's current approach to benefit/risk determinations involves a 3x5 box grid focusing on the severity of the condition under study, whether there exists unmet medical need, what degree of clinical benefit is proven, what risks are identified, and if risk management tools mitigate risk. The FDA paradigm of assessment does not easily translate to physician-patient dialog regarding benefit:risk considerations. However, the European Medicines Agency (EMA) has adopted a qualitative framework for structured decision-making in benefit:risk matters that may better mirror the flow of clinical decisions, so termed ProActURL, an acronym for sequentially assessing benefit:risk through problem definition, identifying alternatives, characterizing consequences, and determining the trade-offs of such alternatives (e.g., new treatment *vs* old treatment *vs* no treatment) [50]. Such sequential approaches do bear resemblance to clinician-patient encounters that may occur when discussing therapy alternatives and warrant further study.

It may be useful for US regulators to consider such an approach since it might enable an easier transition of relevant data to practical application of medical care as well as the potential integration of a benefit:risk statement in the

labeling of all products (i.e., at present, there are separate sections for benefit/indications and for safety/adverse events, but no "rollup" of such factors in US labels).

How such information is relayed to practicing clinicians is of equal importance. Rethinking how post-graduate continuous professional development occurs with regard to imparting clinically relevant information related to a health technology (whether a drug, device, or biologic) may be one element of such a change. The fact that “drug detailing” (sales calls on physicians by drug and device manufacturer representatives) can have both beneficial as well as deleterious effects on safe use practices underscores the lack of a credible, accessible and unbiased resource for single drug education [51]. Surgical specialists spend untold hours mastering a procedure in the operating room, while a similar process for mastering the use of a pharmacologic or biologic agent is a foreign concept even though such a skillset would impact a larger population. Ultimately, regulatory authorities and manufacturers need to jointly find a means of training clinicians on the ever-changing characteristics of their therapeutic armamentarium. As we move forward into the century, clinicians’ information burden will not get any lighter, and the use of tools and workflow enhancements will be of paramount value. Greater effort to develop tools that can summarize salient risks and benefits as well as methods for contextualizing such evaluations into patient discussions and/or use agreements will benefit all parties involved in health-care transactions. Also, making greater use of pharmacists’ time to enhance the considerations of treatment benefit:risk by both clinician and patient will get us closer to achieving both informed prescribing as well as informed consent. These developments will permit a frank acceptance of harm tolerability for any therapy, new or old, that offers to prolong our lives or to improve the lives we have.

The ancient mandate to physicians to “do no harm” can be inferred from the Hippocratic Oath and similar charges, and continuing efforts to assure the safe use of drugs and devices will remain, finally, in the domain of the healthcare provider. Recognizing that few, if any, drugs or interventions are completely safe, it is incumbent upon the prescriber community to have extensive knowledge about the drugs used and to employ a variety of resources to assist in the management of risk from pharmaceuticals. Regulatory agency initiatives do not directly influence the practice of medicine but serve largely as reminders and stimuli; they cannot structure the content of daily clinical practice. The proper balance in the benefit:risk relationship will remain in the hands of individual healthcare providers for the foreseeable future.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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PATIENT CONSENT

Declared none.

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