Docket #02N-0115, Risk Management of Prescription Drugs; Public Hearing

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Comments

1. People are living longer and they are more functional, largely due to benefits of modern healthcare

We are witnessing unparalleled increases in longevity and functionality in the American population. The Global Burden of Disease Study has estimated that women born in the next several decades will live to be almost 90 years old on average, and men will live to be over 80 years old. Perhaps equally as important, freedom from impairment in activities of daily living and from the requirement for institutionalized living is growing each year. Thus, while we attempt to improve the system, we should not lose sight of the fact that it is not a failed system. Rather, it is a successful system with significant room for improvement.

This success is resulting in a burgeoning of two special populations, however. First, many older people are now living with multiple chronic diseases, requiring multiple different types of therapeutics given over the long term. The complexity of therapeutics in this population, with multiple comorbid conditions and the normal age-related decline in renal function, is well known. Second, we simultaneously have a large population of children living with diseases that had been fatal in the past—therapeutics in this population are equally challenging, particularly with the growing recognition that we lack basic information about the pharmacokinetics and pharmacodynamics of therapies in children, not to mention a dearth of outcomes data related to therapeutics.

2. The current system of risk management needs significant improvement

Drugs are regulated in the U.S. to meet two conditions — safety and efficacy — when used as described in the labeling. Drugs are considered either safe and effective for use by a reasonably informed consumer (over-the-counter drugs) or safe and effective under the control of authorized prescribers (prescription drugs). Once the FDA approves a drug for marketing, its use shifts to the professional practice arena.

The approaches used by the FDA to guide the use of prescription drugs typically are limited to communicating with healthcare professionals and others, restricting access to the drug (such as with thalidomide or mifepristone) or, in extreme cases, withdrawing the drug from the market. When a drug is withdrawn from the market, it may reflect inappropriate use of the drug rather than unavoidable safety problems. This raises the specter of whether valuable drugs will be denied approval, or withdrawn once approved, because methods of communicating risk and benefit cannot ensure reasonable safety in use.

The methods used by governments and industry to communicate the risks of drugs clearly are inadequate. This conclusion is reinforced by the landmark Institute of Medicine report on patient safety, which concluded that medical errors cause a large number of deaths. The exact number has been much debated, but it is important to realize that these figures did not include the outpatient clinic. As research begins to bring the outpatient clinic into focus, the complexity of communicating about both risk and benefit is increasingly evident. The Institute for Healthcare Improvement (IHI) has called for a national commitment to reducing adverse drug events, by deploying a medication system that is 10-fold safer.

Our major point for today is that isolated and "common-sense" approaches towards policy in this arena carry a significant risk of failure because of the complexity of interactions inherent in the delivery of therapeutics and the substantial risk of unintended consequences of well-intentioned policies. We believe that policy must by guided by information derived from well-designed health-services research.

3. Much of the improvement needed is outside the direct purview of the FDA—an effective system will require partnerships between the FDA and those who deliver healthcare

As stated above, the FDA has a limited direct role in the system of risk management, since the delivery of therapeutics is in the purview of medical practice. By design, our system allows considerable freedom for the many participants in this arena, including prescribers, pharmacists, nurses, the medical-products industry, consumers of medical products, and, last but not least, the press.

Inadequate *knowledge* clearly is a problem with risk communication. Prescribers tend to be unfamiliar with changes in drug labeling, and most understand only poorly how the medical-products industry and regulatory bodies interact. Little of these two topics is taught in schools of medicine, pharmacy, or nursing, and few practitioners have a systematic method for staying abreast of changes in labeling. Thus valuable risk information often remains undetected by healthcare providers.

A significant barrier to risk communication is the dual roles that drug labeling tries to satisfy: 1) a legal document that may affect a company's exposure to liability in future claims, and 2) a risk-communication vehicle intended to influence practitioners' behavior. The two concepts often conflict, with one achieved at the cost of the other. In an attempt to cover all contingencies, labels contain large amounts of information, only some of which is of higher priority or more commonly applicable. Clearly, drug labeling is a necessary but insufficient tool for risk communication. At a minimum, the information should be prioritized for importance and general applicability.

Prescribers also have grown cynical about drug labels because their Contraindications, Warnings, and Precautions sections often include situations that, from the physician's perspective, represent acceptable (or insignificant) risk. Many drugs used in pediatrics, for example, have a warning against such use solely because they have not been tested in children. In the case of mibefradil, the patients most likely to be treated (those at high risk) were excluded from the premarketing clinical trials. Thus the information that *is* provided on drug labeling may

lack significant data about the context of completed studies and limits to existing evidence that would be useful to practitioners. Quantification of risks would be an important step in this regard.

Attitudes of prescribers play an important role in how information about risk management is received. We are finding that there is often perceived lack of agreement about the basic information, and lack of motivation to change practice combined with inertia. Significant barriers to reaching practitioners, coupled with organizational constraints, seem to have created an environment in which effecting changes in prescriber and patient behavior is complex and difficult.

The modern practice environment creates a serious barrier to communicating risk about drugs, particularly office-based practice. Physicians believe they have insufficient time for each patient encounter, particularly with the increasing number of elderly patients with complex comorbidities and complex, specialized therapies. Because the prescribing decision usually occurs at the end of the encounter and is not a specifically reimbursable action, the time allotted to this decision is compressed. This "time-compressed prescribing decision" also must be made within a fragmented, paper-based system of healthcare delivery. When making the prescribing decision, the physician may be unaware of other treatments (drugs, herbal remedies, supplements) that the patient is taking or of new labeling cautions about the new drug being prescribed. Further, as noted, drug labeling is written in an unwieldy format, and in language that attempts to balance liability protection with risk communication, which fails to connect with the busy prescriber. Finally, financial pressures on healthcare have caused reductions in ancillary office personnel, who could deal with these issues "off-line."

Although the office-based practice needs the most attention, the same observations can be made for hospital-based care. In hospitals, however, teams of people, including clinical pharmacists and nurses, often provide a "safety net" to intercept errors and suboptimal decisions. Again, cost constraints impair the ability of hospitals to provide these support services at the optimal level. Nurses often spend the most time with patients, but the pressures of an increasing workload are at least as serious in nursing, and possibly more so because of staff shortages, as in medicine and pharmacy.

Community and hospital pharmacies face the equal pressures of increased workload and reduced reimbursement. Computer technology has been adopted, in both the pharmacy and physician offices, much faster for obtaining reimbursement than for improving clinical care. One significant difference in pharmacy practice versus medical practice (where prescriptions generally are not financial transactions) is the rapid adoption of information technology (IT) to process prescriptions and drug information. In this case, behavioral changes are motivated on multiple levels, and they carry positive feedback (reimbursement).

Unfortunately, inadequate approaches to assessing evidence on therapeutics have burdened pharmacy information systems with oversimplified alerts that lead to an increase in workload rather than in useful information. This information overload, caused mostly by numerous false-positive alerts (such as drug-drug interactions or drug-dose warnings) and reimbursement-related signals (such as prior authorization or formulary restrictions), compromises the pharmacist's

ability to prevent inappropriate use. The application of expert-systems techniques could help reduce this problem, but this remains an elusive goal. Such a system would need to reflect a more complete computerized clinical record and empirically tested decision rules, because two potentially interacting drugs may be contraindicated in one clinical situation but life-saving in another.

The AIDA model is commonly used to describe the four steps for effective communication. First, the message must exceed a threshold level of perception so that the recipient (in this case, the prescriber) is AWARE of the message. Next, the message must be differentiated from all competing messages to capture the recipient's INTEREST. The recipient then must be persuaded that the intent of the message is DESIRABLE. Finally, the message must spur the recipient to ACTION. Conceptual models such as AIDA provide a sensible context for judging risk-communication efforts — although each step in the process is essential, it is only when action is taken (such as prescribing a drug with appropriate monitoring) that we can say that risk has been communicated effectively.

The primary functional tools used by the FDA to communicate risk are "Dear Healthcare Professional" letters and modifications to drug labeling. These oversimplified approaches to risk communication could be enhanced by using conceptual models such as AIDA. For example, individualizing the message may be essential to meet an *Action* threshold. The "Dear Healthcare Professional" format might be replaced with a "Dear Dr. Smith" format that recognizes the physician's unique practice context and conveys a personalized message. Although the situation is not entirely analogous, clinical practice groups and academic centers have shown the ability to craft practitioner-, patient-, and drug-specific messages to improve prescribing. These messages have been most effective when there is prospective interest on the part of the recipient.

Communication also should be continuous, with timely follow-up contacts to both reinforce the message and convey new information. Although privacy and confidentiality must be protected, if the messages could audit and provide feedback about the movement toward more (or less) desired actions, their effectiveness might be heightened. One example would be to track the percentage of a physician's (or hospital's) patients prescribed a β-blocker after a heart attack.

Although these strategies for risk communication are more intrusive than those used by the FDA, they are widely used and accepted throughout the healthcare system. The research agenda should account for the fact that although insurers use various methods to communicate risk (and benefit), almost no empirical data are available to show which techniques are successful and should be adopted.

Advances in IT provide unprecedented opportunities for improving communication about drug risks. Online entry of prescriptions, with prospective review and feedback from a patient-specific and comprehensive clinical database, represents the "Holy Grail" for communicating risk information. Although prototype systems at U.S. hospitals and Dutch pharmacies have shown remarkable potential for automated medical records (AMRs) to reduce drug-related morbidity, mortality, and errors, a comprehensive and efficient system does not exist. The AMR thus remains a distant promise for all but a few settings. As voice entry or other interface technologies are developed to serve large groups of users, this distant possibility may move closer to reality.

Personal digital assistants (PDAs) for computerized physician order entry (CPOE) of prescriptions offer an opportunity for comprehensive evaluations of prescriptions in real time. Although limited compared with an AMR, the marriage of PDA and CPOE has significant advantages. It could allow online entry of prescriptions with drug-specific warnings (such as drug dosing) and limited patient-specific warnings (such as drug-drug interactions), although it would also require changes in the reporting system to reduce false-positive alerts. Regardless of the technology used, CPOE systems represent the most likely breakthrough in communicating risk about drugs to achieve AIDA goals.

IT also is attractive because it can bring consumers into the risk-communication equation. Consumers are targets of massive efforts to communicate information about effectiveness, evidenced by the billions of dollars spent each year on direct-to-consumer advertising of prescription drugs. If consumers can be targeted to receive information about effectiveness, they also can be targeted to receive prioritized, comprehensible information about risk. The potential for engaging consumers in a balanced, objective approach to communicating risk should be explored.

The attractiveness of IT is not without caveats. First, the privacy and confidentiality issues are daunting, especially if the communication that flows through the CPOE originates with the regulatory body or the drug manufacturer. Second, the liability issues would be difficult under any circumstances, but especially so in a litigious climate such as surrounds drug-injury claims. Third, operational issues have yet to be addressed, specifically the effect of transferring review and adjudication processes from the pharmacy to the physician. The processing of prescription data currently is a major barrier to efficiency in pharmacies, given the problems of false-positive alerts, ineligible recipients, and formulary restrictions that require the attention of pharmacists and technicians. Many of these functions would be transferred to the prescriber in the online environment, with deleterious effects on cost and efficiency.

The best IT system is useful only if it is used, and used properly. Given the fragmented delivery of American healthcare, including the prescribing of drugs, relying on IT solutions may well create additional burdens and challenges. A systematic, empirical assessment of any new technology seems only prudent.

Again, although the FDA has the primary responsibility in the U.S. system of risk management, collaborations with other Federal agencies such AHRQ and CMS, and with other public and private groups are required for development of the most effective tools and processes. The Centers for Education & Research on Therapeutics (CERTs) is one example of a successful public-private partnership that works to identify and address gaps in our knowledge about risk.

4. To the extent possible, policy changes should be based on research.

At the front end, knowledge that can place benefits and risks in proper perspective requires large, outcomes-based trials. Several recent examples point out the difficulty of posing a well-defined risk against a benefit believed to be present due to effects on biomarker surrogate measures. For example, when a statin has a higher risk of rhabdomyolysis compared with other statins, this profile may be tolerable if the statin is shown to save more lives and prevent more strokes than

other statins. If the only greater benefit is a larger change in lipoprotein profile, however, it is nearly impossible to make a rational judgment about comparing a tangible risk against a hypothetical benefit.

Even when good information *is* available to devise a risk-management program, well-intentioned policies based on that information can have unintended consequences. Almost no research has been done comparing the consequences of different approaches to risk-management programs.

A simple example is the degree to which a label transmits the desired information to the prescriber. Empirical work by Dr. Ruth Day has clearly shown that the physical layout of the label is important in terms of information retention.

5. The CERTs are doing research that can inform policy in this arena.

The CERTs program is a national initiative to conduct research and provide education that will advance the optimal use of drugs, medical devices, and biological products. The program is administered by AHRQ in consultation with the FDA. The CERTs concept grew out of recognition that physicians need more information about the therapies they prescribe. At the same time that medical products improve the lives of many patients, significant numbers of adverse events and inappropriate product use seriously impair to the health of others. Guidance on appropriate product use, prevention of errors and adverse effects, and cost-effective use of new and existing products is limited, indicating that health professionals need more complete information about the drugs and biologics they prescribe and the devices they use, and that practices associated with their use should be improved.

To address these issues, Congress authorized the CERTs demonstration program as part of the FDA Modernization Act of 1997. AHRQ awarded the first CERTs cooperative agreements in September 1999; the full CERTs program was made permanent in December of that year as part of the Healthcare Research and Quality Act of 1999. Currently there are seven funded centers. For more information please refer to the CERTs web site www.certs.hhs.gov.

Many of the CERTs are evaluating risk management for drugs that can prolong the QT interval of the electrocardiogram, which carries a risk of torsades de pointes and sudden death. Dr. Ray Woosley, formerly of Georgetown and now at the University of Arizona, has developed an Internet based, international registry of documented torsades cases. Both Dr. Woosley's group and the Vanderbilt group were involved in the critical research showing the minimal effect of "Dear Doctor letters" in attempting to manage the risk of cisapride.

At Duke, we have been evaluating the risk management program for dofetilide. This new drug, introduced for the treatment of supraventricular arrhythmias, prolongs the QT interval and carries a definite risk of torsades. An excellent clinical development program showed the relationship between dose and serum levels of the drug, and the relationship among serum drug levels, QT interval, and the risk of torsades. The program also showed the safety of dofetilide in a high-risk population with left ventricular dysfunction after myocardial infarction, in a large mortality trial. The labeling of dofetilide specifies that is to be started only in the hospital, by practitioners who have attended an educational program on its use.

Although our results are preliminary, we likely will conclude the following:

- Most prescribers have difficulty accurately measuring the QT interval and remembering dose adjustments and drug interactions.

- The uptake of dofetilide by practitioners has been slow relative to other similar drugs.

- Prescribers are more likely to observe recommended precautions and to give the recommended dose with dofetilide compared with other similar drugs.

These results point out the complexity of risk management. In a complex therapeutic environment, labeling may direct prescribers away from better-proven therapies that can be prescribed safely to less-proven alternatives that are not plagued with the same labeling.

Initial observations from this study, coupled with many other observations from the CERTs investigators, have prompted keen interest in evaluating computerized order-entry systems, specifically with regard to drug interactions and adjustment of dosage for renal function. We are finding that there is no easy approach to this issue: the use of a drug (at a given dose or combined with another drug) can be completely reasonable in one clinical circumstance and contraindicated in another.

Because of the complexity and uncertainties of these issues, we have organized a series of "think tank" meetings to develop a research agenda on risk management. The first meeting, Risk Communication, forms the basis for much of this presentation. Critical questions remain, however, the answers to which are fundamental to the creation of informed policy. The second meeting, to be held next week, will cover current issues in Risk Assessment, again with the goal of identifying the critical gaps in the evidence needed to inform policy. Later meetings will discuss the assessment of benefit, how to balance the assessments of risk and benefit for given drugs, and, finally, the role of the media in the presentation and perception of risk information. A final meeting will summarize the findings and put them together into a framework for risk management.

6. Funding for therapeutics research is inadequate.

The best possible research agenda will be fruitless without adequate funding for the research. The Clinical Research Roundtable of the Institute of Medicine has clearly identified funding for health-services research as a major deficit in our national research portfolio. At a time of unprecedented advances in biotechnology, it is sobering to consider the rudimentary understanding we have of the best approaches to delivering the treatment. We sorely need methodological and pragmatic research oriented towards benefit and risk assessment of therapeutics, a framework for depicting those terms in a manner understood by both prescribers and consumers, and effective communication of that information. Without the research, however, the promise of many exciting therapeutic breakthroughs will not be effectively transmitted to the people who stand to benefit.