Risk Management: Issues for Outcomes Research

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What is drug safety? We always say that drugs approved by the FDA are safe, and in the public mind that means they do not have any side affects. They are safe. What does it mean legally? The Food, Drug and Cosmetic Act just says that you will do adequate tests by all methods reasonably applicable to show whether or not such a drug is safe for use under such conditions. Notice that it does not tell you what safe for use is. The problem is that no drug, as you well know, is 100% safe. The FDA has long used a working definition of safety: that the benefits outweigh the foreseeable risks for a specific indication in a specific population, and that is what the drug development program needs to show. So in approving a product, the FDA determines, and this is a very simple way of looking at it, that the benefit of the drug exceeds the risk for that population. This is not about just numerical benefit and numerical risk. This evaluation includes weights or values that are assigned to all those risks and the values that are assigned to the benefit. So this very difficult determination is whether the weight of a drug's benefits is weightier for the population than the weight of the risks. There is another step after a drug is approved—that is, for each patient and each prescriber to make an individual decision based on personal values. You do not have to take a drug. It is not like many other risks that are introduced into society. But for the FDA, determination about drug approval relates to the population.

Now how do we assign these risks and these benefits? In vitro data are useful in the preclinical phase, in early clinical development. We also use in vitro data on carcinogenicity because you cannot do that kind of testing in humans obviously, but otherwise most lab data are not really put into the equation. Also during drug development, animal toxicity data are gathered, and these are mostly used for the safety of the subjects in the clinical trials; what is the proper starting dose? How much can people tolerate? The animal toxicity data, unlike, for example, in the environmental world, would not be used much in weighing the risks at the approval decision for a drug. But, animal carcinogenicity and animal reproductive toxicity are used and that is because we cannot do these specific tests in humans.

Most of the prediction of risk we arrive at when approving a drug is based on human data that have been gathered during clinical trials before the drug is approved. The premarket exposure of people usually is around 2,000 to 10,000 with varying duration, varying dose, and different kinds of concurrent illnesses. The problem with this is the limited power of such exposure to detect an association with an event that occurs at a rate of maybe 1 in 300 to 1 in 1000. The detection ability also depends on the background rate in the population. Many fairly common effects, say those that occur in 1 in 500 people or 1 in 1000 people might not be seen in the premarket exposure. These effects would emerge only when millions of people are exposed to the drug after marketing. If you are lucky enough to observe an infrequent event at all, you rarely have an ability to quantify it or develop any kind of reasonable estimate of the rate of that event.

What we find when we expose people to pharmaceuticals before they are marketed is a huge range of side affects, most minor, some moderate, and some occasionally very severe. To improve this situation we are hoping that new science will give us a real leg up on this. It is not desirable to wait until you have seen a catastrophic event. You would like to be able to predict it from some other data that you have; for example, we are looking at the $QT_c$ interval, which is an electrocardiographic marker of heart electrical system toxicity to predict the possibility of sudden death in susceptible individuals. Similarly, perhaps there are better tests of liver function or liver damage to help us predict which drugs are going to go on to cause catastrophic liver failure and which ones, like aspirin, just raise liver enzymes occasionally. Human biomarkers have some promise.
In addition, there is a great hope that pharmacogenomics, the science of how genetic makeup interacts with drug therapy, will help us identify the sources of human variability that determine why only some people develop problems. Medical people call these reactions idiosyncratic, which is another way of saying we do not know anything about the cause. But there must be a reason, a scientific reason why some people get ill from drugs. It is not just chance, it is simply that we do not know the reason and so we dismiss it as idiosyncratic.

Pharmacogenomics may help us determine more of the metabolic differences in humans that lead to drug toxicity; may provide and have provided actually in some cases, markers for catastrophic risk that some people with a certain gene or lacking a certain gene are the ones that will get a catastrophic risk from a pharmaceutical; or may help us identify the people who will not benefit at all from a drug so these individuals are not exposed.

Drug/drug interactions are another way of predicting risk, which is a partial success story. In the past decade, we figured out how drugs are metabolized, in vitro and in small human studies, and pick out the really bad actors drugs, the drugs that are going to inhibit the metabolism of other drugs. Many of the drug withdrawals over the past decade have related to drugs that cause drug/drug interactions. So the new science may help us quantify that risk a lot better. But we are not there yet.

Now what about predicting benefit of a specific pharmaceutical? As you all know we do that from randomized controlled trials and there are problems with these trials. At a minimum they show us whether or not the drug works. and that is more than you can say about a lot of other study designs that are not randomized controlled trials. But they lack generalizability to the population that is going to be exposed to the drug. They often do not measure all the domains and this is really a problem when you are trying to weigh benefit against risk and you really have not measured all the benefit. What really bothers me is that we look at the population means; we do a statistical approach to benefit, and we say there is only, for example, 7% more benefit in the treated population over the placebo or active control population. The problem with this concept is that it says little about responders. It is true for a cancer drug, for example, that perhaps you only get one chance and so it is appropriate to look at the population mean. But for most chronic diseases, clinicians try one medi-

cine and, if it does not work, they try another medicine. This gets back to pharmacogenomics. Some people respond to a drug and some do not. and so when we are looking at benefit, for many drugs there is probably a small proportion of people who benefit greatly, but this translates statistically to a small mean benefit to all.

So, when we approve a product, we have made a prediction that the benefit is going to exceed the risk. There are some problems that can develop. We may have done a bad job; we may have missed some of those rare serious adverse events. We did not have any biomarkers that predicted them and they show up afterward. Another problem is what the Institute of Medicine has called medical errors. I was pleased to be able to go through your poster session downstairs and, I must say, it was a hair-raising experience, to see in some cases, for serious risks, that only 2% of the prescribers followed the treatment recommendations. The message here is that medical errors, misuse of the product in some way or another, can really tip this balance over and the drug is going to start causing more harm when it is actually out there than was predicted because we did not predict how this product was going to be misused, in a manner of speaking. A drug can actually turn out to be less safe if it is used in a way that decreases the foreseeable benefit. For example, using a drug recommended for a sick population in people who really are not very sick, who have less to gain and more to lose, diminishes the benefit/risk proportion. Coprescribing with contraindi-
cated drugs increases the risk. Or, and this is the one that gets all the press, if the actual risks are greater than predicted; in other words, if we miss something in our predictions.

There are values: some weights on that balance that you do not think of, that cause risks to weigh more for a newly approved drug. This is a well-known fact about risk perception: anything strange or unusual or new or whatever is perceived as more serious or severe than something we are accustomed to. For example, the nonsteroidal anti-inflammatory agents are probably the most toxic drugs we have on the market for non-life-threatening conditions, and yet, people do not really think much about their risks.

When you look at that balance and you think about the risks, one way we can keep that benefit positive is not just by sitting back and waiting for things to happen but by actually trying to influence or manage how the drug is used or manage some of those risks. You could make interventions that maximize the benefit of the drug; you could make inter-
ventions that minimize the risk of the drug, the goal being to a positive benefit/risk analysis so that the drug remains safe in terms of the meaning that we have given to safe.

What are the sources of preventable risks? It is hard to manage inherent risks, but what about preventable risks of drugs? The Institute of Medicine has done a whole report about medical errors called “To Err is Human”: errors clearly are a large source of drug risk. Probably the greatest source of risk is inappropriate or contraindicated prescribing, prescribing in the face of a known elevated risk. A prescriber may have good reasons for this, as I will get into later, or it may be pure ignorance. Another source of risk is drug/drug interactions. Another source is failure to appropriately monitor the patient after being put on the therapy to make sure risks are controlled properly. and another, which gets a lot of press, is a mix-up. Medical mix-ups occur when one drug is accidentally substituted for another drug, and the patient may die because he or she was given something completely inappropriate. Another source of decreased benefit/risk is not managing the benefit side properly. Using a drug with a lot of risks in a low benefit population is really changing that balance, and again that can be done by ignorance on the part of the prescriber or may be done with full knowledge. But we hope that it is done with full knowledge of the patients, of the risks they are assuming for the benefits might accrue to them; off-label use of this kind of falls into this category. The patient can make errors of use that up the ante; for example, patients may give the drug to a neighbor or they do not know about drug/drug interactions. Poor adherence, which is rampant among patients, often will expose the person to all the risks of the drug, with decreased benefit.

Risk management in the pharmaceutical setting is intended to alter behavior patterns that lead to excess risks, these preventable risks. Examples include avoiding an at-risk population. A good example is the risk management program for thalidomide. Thalidomide is a major human teratogen. A very stringent program was put into place when thalidomide was approved that is intended to prevent pregnant women from taking thalidomide. Accutane® is a widely used acne drug with the same problem. It is a major human teratogen and pregnant women should not take it. We discovered a couple of years ago women were starting on Accutane when they were already pregnant. This is a medical error that should never happen. And, therefore, additional steps were put into place to make sure that no pregnant women take Accutane. That program is new and we will see how it works over time. But that is an example of trying to proactively manage a risk. With Clozaril® we tried to avoid severe blood dyscrasia by monitoring the white blood cell counts. But that did not happen just by putting it in the label and saying monitor the white blood cell counts. So a program was put into place: you now cannot get a prescription unless you have a white blood cell count performed—very simple, an aviation model, fail-safe, and it worked. We have the outcome data as far as adverse event reports of dyscrasia; it worked.

Household safety is another issue with pharmaceuticals, as more and more home health care occurs, there are more and more substances around the home that used to be locked up in the hospital pharmacy. What do we need to do to keep children from being killed by getting into these substances? There are common-sense practical steps to minimize that risk. The FDA has tried to maximize benefits with the weight loss drugs by targeting a severity level. This is widely disregarded by the practitioners, as are many other label recommendations. Another way to maximize benefit might be to avoid off-label use or, as we talked about with pharmacogenomics, perhaps targeting subpopulations that would really benefit from the drug.

If you are contemplating an intervention to minimize risk, you need to ask a number of questions. First you must ask when you are confronted with a risk: is it really associated with the drug? What is the level of evidence that the drug actually causes this risk? Often people get really excited about a risk that turns out not to be associated with the drug. Then you have to ask yourself, how large is this risk, if associated with the drug? For example, with Accutane we knew that women who were exposed within a certain period of gestation would have a very high probability of having a child with developmental defects. On the other hand, there has been a lot of discussion about Accutane and neuropsychiatric problems in people who are taking the drug, including depression and potential suicides. Is this associated with the drug? We do not have very much information about Accutane and neuropsychiatric side effects. So we are still in the phase of determining association for that particular side effect. Then you have to ask also, what is the role of medical error in causing the risk or is this an inherently nonpreventable risk? If this drug were used perfectly, according to every guideline, would this risk still be there? For example, bone marrow depression with chemotherapy is like this: we just
do not know how to use those drugs in a way that avoids bone marrow toxicity.

Then the next question you would have to ask is, what would be the benefit of the intervention? Again I see people who do not go through these steps. We need to measure the benefits. What is the intervention intended to accomplish? Often I see people proposing interventions that are not going to accomplish controlling a risk, simply because they are worried. Then you have to ask, how would I tell if I have succeeded? What is an acceptable level of success with the intervention? And very importantly, how do you evaluate that? It is no good putting in place various schemes if you cannot really tell whether they work or not, and obviously, to do that, you need some baseline information.

Next you have to talk to yourself or your group about the cost of the intervention. There are many kinds of costs, not just dollar costs. There are operational costs to whomever is doing this, of whatever intervention it might be; there is a burden on the health-care system. We know this is true with thalidomide and we know this is true with Accutane, but we think from a societal point of view and I think the companies believe as well that preventing damaged infants is worth this cost and burden. But there is a burden of time and efficiency loss in an already burdened health-care system. There also may be loss of access to the drug of patients or prescribers and this must be taken into account, and there may economic costs or loss of privacy on the part of the patient. This is something we have to weigh very carefully and think about. Another thing you do not think about always but needs to be considered—are there unintended consequences? We believe that we have already seen unintended consequences of risk management programs for pharmaceuticals. One new pharmaceutical was surrounded by a very careful program to manage a particular risk. The program added some burden, and therefore the practitioners chose a potentially riskier drug that does not have any burden associated with it. They prescribe that drug instead. There are other kinds of unintended consequences. We can burden the health-care system in a way that could create other risks, other errors, and other mistakes. So you really have to think through all the unintended consequences as you are contemplating an intervention.

Often, we do not really understand the basic or fundamental cause or source of the risk, and it is really hard to treat something if you do not have the proper diagnosis. So if you think it is one cause and it is really another cause, you are not going to get any value from your intervention. An example is in the drug Propulsid, which was withdrawn from the market after it was associated with sudden death. When we looked at the use of the drug in practice, in some settings half the patients prescribed Propulsid were taking contraindicated drugs or had contraindicated conditions. Propulsid was a drug for heartburn, so it is unlikely that practitioners thought their patient absolutely must be prescribed this drug, although the drug was used for other indications, so that is possible. Why did it happen? Were the prescribers unaware of the contraindications? Was that the root cause? Did the prescriber not believe the warnings? We have certainly heard that a lot. Practitioners tend to be anecdotal: I have never seen it in my practice, so it does not happen. Right? Or did the prescriber decide the contraindication was not relevant in this case? Or did the patient receive many different prescriptions from different prescribers who in fact did not communicate with one another and so the interaction occurred because of a problem in the health-care system? Until you understand the sources of the scenario, you really cannot intervene properly.

We have lessons in safety from other fields that can be applied, and this does not have to do with the FDA; this has to do with the health-care system as a whole. The best tools are built in; we know this from aviation and we know this from other safety areas. They should not require a lot of user effort and thought. A risk management intervention should not require a lot of effort, because people are going to forget to do it. Approaches that build safety into systems are vastly preferable to piecemeal solutions. Standardization is one of the major safety tools, and that is true for all different disciplines that have safety programs that have looked at safety. Forcing functions, in other words, constraints, are very effective and that is an example of thalidomide or Accutane where there are actually constraints built into the system that would make it really, really hard to dispense those drugs to a pregnant woman. That is not saying that it will not happen, but it would be really, really hard. That is a constraint.

Redundancy is an important aspect of safety as well. For health care, you need to avoid reliance on memory and avoid reliance on vigilance. However, the professional model that health care uses is memory and vigilance. It is not a systems approach; it is a “professional” approach where it is posited that each professional will remember everything. Unfortunately, in today’s world of pharmaceuticals, that is not possible. It is not possible to remember everything; there is too much information. Back when
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we just had morphine, penicillin, sulfa drugs, and a couple of others, it was possible, but not now.

Anticipate the unexpected. At the FDA, we agonize over mix-ups. Who would have thought that people could mix up some of the names of drugs that have been mixed up? One is a parenteral formulation and one is a pill, and how could you possibly get those mixed up? Well, you can.

Improve access to timely and accurate information. At the FDA we realize that one of the deficits is that the prescribers do not have that important information in front of them at the time of prescribing. They do not have information about the contraindications and what else the patient is on; they are relying on memory, they are relying on vigilance, and it is not enough.

Do our current risk management programs, the few that have been put in place for pharmaceuticals, fit the paradigm? Do they have the ideal characteristics? No. Most of them rely on constraints, but when we evaluated them, they are effective. Constraints are effective. But they are burdensome. We cannot have hundreds of constraint systems out there, the constraints themselves will cause other errors, and they will have unintended consequences. They are burdensome and they lack a standard approach. So what have we learned about managing the risks of medicine? We have learned that for the health-care community, the way the drug is set up at the initial launch is important. Practitioners or prescribers will respond to that initial information, maybe because that is the only time they read it. Late follow-up with “dear doctor” letters or other information, directed at practitioners, no matter how intense it is, has much less impact. It is really hard to change a behavior once it is established. That drug interaction information is not followed is a total understatement. Drug/drug interaction knowledge appears to be fairly scanty among practitioners and I have considerable sympathy for this. I blame in part the clinical pharmacologists who use all those little alphanumeric acronyms for enzyme systems! Communications after practice patterns are established are not completely effective in changing practices, even though those practices may lead to fatal results. Practitioners resent burdensome programs. We need evaluation, and we need it from the outcomes community. We need to figure out what are the benefits when you put a program like this into place. What are the costs? What are the unintended consequences?

Society’s dilemma is that while we all share common goals of minimizing the risks and maximizing the benefits of drugs, we lack a consensus on how to achieve this. Many people feel (but I do not know how much data they have) that if we controlled error better we would actually save a lot of money in the health-care system. I think that is probably true, but I have no data to back that up. How much are we willing to pay? Even if there would be an ultimate return on investment, there is going to be an up-front cost. How much are we willing to pay in money, how much are we willing to pay in loss of autonomy for health-care practitioners? That is really a big issue, as you know. How much are we willing to pay in time and effort in an already burdened health-care system, to minimize risk, to maximize benefit of drugs?

What about irreducible risk? This is a values question that our society appears to be incapable of having a really informed debate about. How much is tolerable? How much irreducible risk of a drug is tolerable? Who should decide? At the bottom line, we feel that a patient, and prescriber, should decide together for that patient. But who should decide globally?

In summary, continued drug marketing depends on continued favorable benefit risk analysis. Our prediction at the time of approval may not be borne out by the facts when millions of people are exposed to a drug. But the good news is that we can be proactive in minimizing risk and maximizing benefit. We do not have to sit passively by while this unfolds. Interventions work best before practice patterns are established. Additional tools are needed and evaluation of outcomes must be incorporated into risk management programs.

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