

FDA's Drug Approval Process: Up to the Challenge?

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Testimony

Mr. Chairman, thank you for the invitation to appear before the committee. Today I want to tell you why I believe the FDA's mission is becoming increasingly complex. But with this complexity has also come many new opportunities to improve medicine. And I want to tell you why I believe that, as the sophistication of FDA's mission continues to increase, so must the tools it uses for accomplishing its work. Especially when it comes to drug safety.

To acquire these tools, FDA will need new resources that allow it to make better use of advances in information tools for monitoring the safety of approved drugs.

The good news is that FDA is doing some of the right things right now, albeit in small pilot programs. The bad news is I believe our current political discussion seems to ignore these opportunities in lieu of some more visible changes. These visible changes will have far less positive impact on drug safety, and will limit access to medicines. They will make drugs more expensive and less likely to reach patients who need them.

Mr. Chairman, we are living in a remarkable time of scientific progress. When I was at the Food and Drug Administration and the Centers for Medicare and Medicaid Services, a lot of my time was spent looking at the policies these agencies followed in the evaluation of new medical technologies.

When you look at the technologies that have become available, even over a short time, it becomes immediately clear that improvements in healthcare follow a stepwise progression. The introduction of new medical technologies, the realization of better ways of practicing medicine or of avoiding illness, all leads to small improvements in medical care that over time, and aggregated together, give us major improvements in health.

You can see this, for example, in the strengthening of our understanding of how the immune system works and the advent of our ability to manipulate it in order to produce drugs that can replicate our own immune processes such as monoclonal antibodies.

You see it when you look at the mortality statistics around breast cancer, were successive product introductions from Taxols to Aromotase Inhibitors to drugs like Herceptin, each had a small impact that over time and taken together, led to significantly better odds of surviving the disease.

Or even more recently, you see it in our improved understanding of the genetic basis of

disease. Already, if you look at the early drug pipeline being submitted to FDA – the investigational new drug applications -- you see many drugs that were derived in part or entirely through techniques of genomics and proteomics, the latter of which is the science of how genes make proteins to carry out all of our complex human processes.

All of these new medical products are the result of advances in our science of biology. Past medical products have taken decades and even centuries to be made manifest on the heels of the scientific discoveries that enabled them. Today's FDA is already seeing in early applications dozens of drugs derived wholly or in large part from science developed just several years ago.

This acceleration in time between the development of a science and the creation of products that capitalize on it is giving us an awful lot of new opportunity – to find fundamentally better ways to treat disease. But it also presents the government agencies that evaluate new medical technology with a lot of challenges, especially the FDA.

More and more of the products the FDA is seeing are very novel, and, as such, the agency has no reference point. So in more and more cases regulators are embarking on new ground each time they pick up a new application.

In the old days, drugs worked through fairly similar mechanisms. Now the same review division – lets take the cancer division – can simultaneously be reviewing a monoclonal antibody, an antisense drug, a molecule targeted to a kinase receptor, a radiolabeled antibody, a cancer vaccine, and a traditional cytotoxic cancer agent, the kind of drug that killed everything a little but hopefully killed the cancer cells a little more.

In fact, I remember talking to the head of the cancer division on just such a day.

On top of all this, the FDA has more factories to inspect, more patients using more of these medicines more quickly after they are first approved, and more potentially dangerous imports seeping through our borders.

I believe the scientific challenges posed by new medical products will continue to mount, but I also believe that this is good news, because novel drugs invariably give us novel ways to fight old disease. And many of today's medicines are simply far safer and far more effective than those that came before.

But as the science gets more intricate, more advanced, our tools for evaluating it need to get more creative as well. This is especially true when it comes to how we evaluate the safety of new drugs.

Understanding the full scope of any drugs side effects is the challenge, especially understanding them early.

Every clinician who prescribes medicines has seen adverse drug reactions -- the unintended and harmful effects of drugs. Human biology, after all, is conservative,

meaning our bodies reuse a fairly small set of very similar molecular processes to get all of their jobs done. It follows that any drug that is active in blocking some molecular process in order to have its desired effect, will also block the same molecular processes in other parts of the body, parts that could lead to an unwanted side effect. So there is no such thing as a safe drug.

The FDA's job is not to guarantee 100 percent safety. It's to approve medicines with an appropriate risk-benefit ratio and remove unreasonably unsafe drugs when necessary. The baseline isn't the perfectly safe drug, but the drug with benefits that outweigh reasonable risks. Congress has given a lot of thought to the laws that set out these parameters, amending the FDA's statute more than a hundred times. The system that our resulting law contemplates always took measure of the simple scientific truth that there's no such thing as a completely safe drug. What has changed today are not the safety of medicines but the acrimony of our public discussion of these things.

Today, the data that medical reviewers at FDA receive in conjunction with the approval process for new products are from highly structured clinical trials, carried out on homogenous populations of patients that are carefully screened and pre-selected and then given new drugs under special protocols. There is little chance such trials will ever provide a complete review of how a new treatment will perform when it is used in a much broader variety of patients in real world clinical settings.

Recent proposals to lengthen clinical trials, or require them to include more patients, will add to their cost and hence the cost of drug development and eventually the list price of new drugs. It will limit access to new medicines. But it will not assuage today's safety concerns, and it will never unearth the kind of rare side effects that were eventually revealed with Vioxx, or even yesterday in the case of multiple Sclerosis drug Tysabri.

Patients are rightly angry about these events because they want safety questions to be uncovered and resolved much sooner. They don't want to have to wait many years.

The good news is that there are better ways to achieve the environment of improved drug safety we all desire, while not sacrificing on the scientific progress we all embrace. In particular, information technology, properly deployed, will enable FDA to pursue fundamentally better ways to monitor the safety and effectiveness of new medical products after they are made available on the marketplace.

These are things the FDA is already doing a little of, but needs to be doing much more.

Right now, when it comes to drug safety, the FDA relies on others to undertake the time and cost of monitoring by sending news of potential problems to the agency. This passive reporting system leaves FDA dependent upon busy doctors to fill out lengthy drug safety reports that are used by the agency to identify and track potential drug side effects.

Taken together, this passive reporting process is slow and expensive, and of course, woefully incomplete. Most of the reports FDA ends up receiving are actually delivered

not by doctors, but by drug makers, who hear about side effects from physicians, often while on sales calls.

So far, fixes to our system for monitoring drug safety have all focused on making this antiquated system work a little faster, by adding only a veneer of sophisticated information tools. For example, more of the forms that doctors and manufacturers complete are now fully electronic. But doctors still have to take proactive steps to enter the information by hand and evaluated by time-consuming, human intervention.

As a result, information is made available to FDA slowly, and takes even longer to analyze by the agency's trained personnel. Very subtle side effects, especially medical problems that occur naturally in a large population can take years to recognize and fully understand.

FDA needs systems that allow it to collect more information about a drug's use in real world, and in some cases real time clinical practice, and to use this information more effectively. This requires two simultaneous efforts:

First, tools for detecting and collecting more safety information more quickly at the point of care in order to detect potential problems earlier.

Second, resources for making better and more frequent use of practical clinical data culled from real-world use of drugs in order to conduct more precise and faster follow-up studies of potential safety problems.

Both efforts require FDA to have better tools for collecting health information electronically and then using information tools to be able to access and manipulate this information.

As electronic medical records and other IT systems gain wider adoption in healthcare, these kinds of opportunities will be more easily accessible. It behooves us to implement drug safety reforms that envision and accommodate these opportunities, rather than implement more expedient but fleeting fixes to our current -- inefficient monitoring system that are predicated on an old way of doing things.

Consider this scenario: A new drug is launched that has a certain rare toxicity to the liver. A real-time surveillance network might eventually be able to detect subtle elevations in the liver enzyme tests of patients who were started on the drug and also happened to have blood work drawn around the same time. If enough of these signals were detected, it might alert FDA that there is a potential liver problem, and allow the agency to intervene before a patient experiences more permanent harm.

Under our current system, such a side effect might go unnoticed until a few patients developed severe liver failure. Even then, it might have been hard to link the problem to the medicine without taking months to go back and review the medical record of many thousand of patients who were started on the same medicine.

While more widespread use of these systems requires greater adoption of electronic medical records, there is already a critical mass of these systems. A lot that can be gained by conducting real-time surveillance on the existing IT infrastructure inside many large healthcare networks and academic centers.

FDA has already struck collaborations with some of these networks, including the Veterans Administration hospitals and Columbia Presbyterian Hospital in New York. Expanding these efforts will require additional funding.

The second step is developing more proactive determination tools to complement better detection systems. These are information and analytical capabilities for evaluating potential safety signals and for establishing a causal link between a drug and a suspected side effect.

Efforts to make better use of electronic healthcare information to more easily conduct practical studies, for example, are already well underway inside FDA and need to be dramatically expanded on if our safety infrastructure is going to keep pace with the expanding scope of our scientific opportunities in medicine.

In conclusion, Mr. Chairman, FDA has already taken some steps to try and create more active and proactive surveillance tools. With improved resources for conducting this kind of surveillance, as well as resources for conducting large simple safety studies in collaboration with product developers and healthcare networks on newly approved products, FDA can improve its safety-monitoring program without burdening the approval process.

With all the advances recently made in the science behind discovery of new drugs, there is little reason we should not be investing commensurate resources in bringing 21st century science to the task of ensuring their safety.