Margaret A. Hamburg, M.D., Commissioner of Food and Drugs - Remarks at the Massachusetts Medical Society

Remarks as Delivered of Margaret A. Hamburg, M.D. Commissioner of Food and Drugs at the Massachusetts Medical Society's 2010 Shattuck Lecture
May 15, 2010

Innovation and the FDA: Past, Present, and Future

Good afternoon—and thank you so much for inviting me to be here today. What a pleasure it is to be here with distinguished doctors and scientists.

As Dr. [Jeffrey] Drazen has noted, this Lecture is a great tradition that stretches back more than a century, and it is my honor to be a small part of that tradition today.

The U.S. Food and Drug Administration also has roots that stretch back more than a century, to the Pure Food and Drugs Act of 1906, which was signed by President Theodore Roosevelt. This is the law that first empowered a humble office in the basement of the Department of Agriculture to protect the nation's supply of foods and drugs.

Since then, American medicine has transformed our understanding and treatment of many diseases, reducing suffering and saving many lives; technology has reshaped our approach to societal challenges; and increasingly complex threats have forced us to think in new ways about science, health and safety.

Alongside—and in response to—our changing world, the FDA has grown and adapted, as well … taking on new responsibilities and playing a critical role in promoting innovation and medical progress.

Today, I'd like to talk a bit about the history of the FDA, and the role our agency has played and continues to play in facilitating the intersection between innovation, evidence and medicine. While hopefully a topic of interest to this group, I want to discuss this as more than an academic exercise.

This is on my mind because a series of lawsuits filed against the agency would, if successful, substantially roll back the agency's ability to assess and assure the safety and effectiveness of medications, vaccines, and medical devices.

Perhaps it is ironic that I come here today to speak to one of the most respected medical societies in the country—in the world—and my remarks are triggered by legal concerns, Nonetheless, these lawsuits raise a number of crucial and timely issues for the FDA and the field of medicine … and can serve as a springboard for a broader discussion about the FDA's role in the future of innovation as well.

So with history and these lawsuits as a backdrop, I would like to offer a vision—organized around progress in the field of regulatory science—for the FDA and innovation in American medicine.

Back in 1902, the Martin H. Smith company advertised for a “remedy in the treatment of coughs, bronchitis … asthma, laryngitis, pneumonia, and whooping cough.” According to the company—and I quote: “From scientific investigations in hospitals, clinics and sanitariums and the personal investigations by prominent physicians, no other preparation has more successfully withstood such critical scrutiny. No other preparation has had its therapeutic value more thoroughly defined or better established.”

What was this wonder drug, you might ask? It was heroin.

At the turn of the century, advertisements like this one were common. Companies marketed their "patent or proprietary medicines" with a variety of unproven claims. Some were potentially deadly—and others just sugar water.

But it took decades for American medicine to emerge from what pharmacologist Louis Goodman called a “therapeutic jungle.”

As the years progressed, important scientific advances in pharmacology, toxicology, and clinical research, were central to this transformation. The FDA embraced these advances—insisted upon them, in fact—and helped pull medicine into the modern era.

And the agency was aided in this by two key laws.

In 1937, a Tennessee drug company manufactured an elixir of sulfanilamide mixed with diethylene glycol. The company tested the product for flavor appearance and fragrance, but at the time, the food and drug laws didn’t require toxicological analysis before sale … 105 people died in 15 states in just two months from the elixir, leading Congress to pass the Food, Drug and Cosmetic Act the following year.

The law established that drugs intended to prevent or treat disease had to be shown to be safe for use as labeled and that the manufacturer had to submit the safety data in an application to be reviewed by the FDA prior to marketing.

This law ended the practice of companies marketing new proprietary mixtures of a wide range of untested ingredients to treat all manner of diseases. For the first time, pharmaceutical companies had to demonstrate at least that products were safe before they could market the drug, take out advertisements and seek sales.

At first, it was unclear to industry, scientists, and the agency what safety really meant. Gradually, the fields of pharmacology and toxicology began to answer these questions. Standardized assessments were developed. And as these advances were incorporated into FDA’s premarket review, they became standard practice across the pharmaceutical industry.

Many of you may be aware of the defining case of thalidomide—the medication that was widely marketed in Europe as a sedative and recommended for nausea for first-trimester pregnant women.

The drug turned out to be highly teratogenic, and thousands of babies across Europe suffered from phocomelia, a devastating birth defect that results in the failure of the long bones of the limbs to develop.

But the drug was never approved in the United States. News reports attributed FDA's action to the perceptiveness and wisdom of a single reviewer at FDA, Dr. Francis Kelsey.

Dr. Kelsey refused to sign off on the drug's safety and was awarded the President's Award for Distinguished Federal Civilian Service from President John F. Kennedy in 1962, a well-deserved honor.

As Professor Daniel Carpenter's recent book on the FDA details, Dr. Kelsey held up the approval of thalidomide not out of personal skepticism … but because its sponsor failed to conduct basic tests of pharmacology and toxicology that were becoming accepted as necessary for safety review at the time.

For example, the company offered one study that had compared the drug to a competitor based on its overall weight – not based on its pharmacological activity. Dr. Kelsey was a distinguished toxicologist as well as a pediatrician, and this study was not persuasive to her; nor was it persuasive to her colleagues at the FDA or to experts in academia with whom she consulted.

In a fundamental way, it was the embrace of modern, innovative scientific methods that kept thalidomide off the market and protected the American people.

It was no coincidence, then, that in 1962, Congress passed another law that had major consequences for FDA—and for American medicine.

For the first time, Congress required drug manufacturers to demonstrate before marketing effectiveness of each use for which the product would be indicated. More specifically, the new law required substantial evidence of effectiveness, and more importantly, that the evidence be based on "adequate and well-controlled studies.

This requirement has changed the face of modern therapeutics by dramatically raising the standard of evidence and the likelihood that a marketed drug will really work.

The law emerged from broad concern over the state of the market for pharmaceuticals. At that point, companies were required to show that their products passed basic tests of safety, but there was still wide latitude for marketing for many different uses, and no explicit standard for demonstrating that the products did indeed do what they were supposed to do …which meant that determining the benefit-risk balance was very difficult.

In some cases, unproven drugs had supplanted those with known effectiveness. For example, Deprol, an addictive tranquilizer, was widely promoted to general practitioners to replace existing drugs for depression, even though there was no evidence it was effective.

Potent psychiatric drugs like Thorazine, Mellaril, and Librium were widely promoted for minor conditions, even in pregnant women. Mellaril, was promoted to general practitioners as good for insomnia, pregnant women anxious about childbirth, "vague digestive disorders," and "tense, nervous patients seen in everyday practice."

Many ineffective drugs also had serious adverse effects, subjecting patients to harm without any benefit. One such drug was diethylstilbestrol (DES), promoted to prevent miscarriage despite a large randomized, controlled 1953 study showing DES to be ineffective for this use. By the time the devastating, multi-generational reproductive effects of DES became known in the 1960s and 1970s, 5 to 10 million American women and their children had been needlessly exposed.

Increasingly, clinicians and pharmacology experts started to complain that there was little evidence to support the use of many medications in clinical care.

The passage of the 1962 legislation marked an important change. From then on, FDA had to review claims--and the data supporting them--and conclude that effectiveness had indeed been shown, before the drug could be marketed.

For drugs already on the market in 1962 based on FDA's prior review of their safety, sponsors had to now submit evidence of effectiveness to the agency.

FDA turned to the National Academy of Sciences for help with reviewing this massive amount of information. The Academy found that 70% of claims it reviewed could not be substantiated. Almost one-third of all marketed drugs lacked even a single effective use and were removed from the market.

As FDA set standards for effectiveness, for the first time, many companies began planning and implementing large randomized controlled trials.

Major therapeutic breakthroughs resulted, including, for example, the use of beta blockers after a heart attack to decrease mortality, a variety of well-tolerated antihypertensive agents that have had a major effect on stroke and other consequences of hypertension, use of ACE inhibiters to improve survival in patients with heart failure, and a host of other therapeutic advances in cancer, AIDS, and many other areas.

Because of the evidence now required for FDA review, the best drugs, rather than the most aggressively marketed drugs, could rise to the top.

In other words, the increasingly rigorous standards of the FDA created the conditions for innovation and progress in the pharmaceutical market.

It is worth pausing to recognize what American medicine and FDA have together accomplished. We know that hundreds of medications work for thousands of indications. We also know that many drugs do not work for other indications. In fact, it is difficult to think of another area of medicine where this level of evidence underlies clinical practice.

Now our challenge is to continue to move forward.

So let me now turn to the two cases that I mentioned earlier … lawsuits that challenge our agency's ability to review the safety and effectiveness of products before marketing.

In the one case, a drug company is contesting the agency's authority to require pre-market review of new uses of already approved drugs before the company can promote the uses to patients and physicians ... the so-called "off-label" promotion issue.

In the second, tobacco companies are challenging FDA's ability to prevent companies from marketing products as safer before reviewing the evidence.

In both cases, the companies argue that FDA's pre-market review violates their First Amendment right to engage in free speech. According to these arguments, companies have a constitutional right to disseminate health claims about their products without first submitting evidence to FDA demonstrating the accuracy of those claims. They argue further that FDA may step in to stop such claims only after it can produce evidence sufficient to convince a court that the claims are false or misleading.

Developing such evidence would be very expensive and time consuming. Moreover, the evidence of ineffectiveness or harm would emerge only after many patients may have suffered avoidable serious adverse effects.

Without question, these legal challenges, if successful, would turn back FDA's proactive role in American medicine, and jeopardize the safety of patients as well as the future of innovation and medical progress.

This is because nearly 50 years after the 1962 amendments, FDA continues to play a critical role in evaluating new therapeutics in the medical marketplace.

FDA helps companies design trials to answer key questions of safety and efficacy.

FDA insists that companies provide all available data for review. This means not just the data that best supports their application, but all data … and a failure to do so can result in criminal penalties.

FDA—uniquely among regulators in the world—then reviews the raw patient-level data from clinical trials prior to approval.

And, with the input from our own scientists and advice of medical experts from around the country, FDA then has the authority to set the terms of use for medications based on science and evidence.

I think the facts speak for themselves. Removing these protections would ignore the lessons of history.

I want to note that some of the arguments aimed at limiting FDA's authority to regulate the off-label promotion of drugs are improperly cast as FDA interference in the practice of medicine. But it is never our agency's goal to limit a physician's opportunity—or obligation—to provide the best care for his or her patient.

Our concern is simply to ensure that health care providers have options for treatment and care based on the best possible evidence for safe and effective use.

It may be impolitic, at today's event, sponsored as it is by the Massachusetts Medical Society, which publishes the New England Journal of Medicine, it is to address whether the peer review process can substitute for FDA's review.

But I would like to consider this issue head on, because some have suggested that with the increasing number of medical journals, FDA's role is no longer necessary.

Peer review is an essential part of scientific dialogue, and medical journals play a critical role in shaping the field of medical research. However, peer review is not a substitute for a strong FDA.

FDA's physicians, pharmacologists, toxicologists, chemists, and statisticians spend thousands of hours reviewing the full set of original data on a product and do not simply rely on summary reports provided by the manufacturer; they frequently request additional data from sponsors.

Peer review, on the other hand, is generally conducted by three experts, and involves only the study under review. According to one survey, peer reviewers spend an average of three hours reviewing an article. They do not reanalyze the original data supporting the report, nor do they have access to the study protocol.

Over time, the peer-reviewed literature supports progress in the evaluation of medications and other interventions. However, positive studies are still far more likely to be published than negative studies, and any one study can leave a misleading impression.

Recently, journal editors themselves are among those raising concerns about such issues as ghostwriting, the reporting of partial study data, the inclusion of fraudulent data, changes to primary outcome measures, the inflation of positive results through inappropriate statistical analyses, and the publication of positive results more than once. Surely this is not consistent with the high aspirations of the medical profession and hard-won advances in evidence-based progress in medicine.

I fear that if FDA's role is weakened, many companies will seek to promote a wide variety of drugs for many different uses without adequate evidence. Individual studies will be trumpeted as proof of effectiveness, without the benefit of a full review of data by an independent entity.

Some of these promoted uses will likely be fine and of value, but others will provide no benefit at all for patients. For others, the benefits will be outweighed by the risks. Moreover, companies with truly innovative and effective products may have a difficult time penetrating the confusion.

And true medical progress may slow as American medicine heads back to the so-called therapeutic jungle.

Tobacco is a little bit different. In this case, a loss in the pending lawsuit would leave our country vulnerable to a repeat of the "low tar" fiasco, one of the most costly public health charades of the 20th century.

Millions of Americans switched to "low tar" cigarettes instead of quitting altogether when there was never any evidence that these products provided a health advantage. Congress intended FDA's new role in evaluating so-called "modified risk" tobacco products to prevent such a tragedy from happening again.

But rather than turn the clock back, we should look forward to a new paradigm of scientific efforts to support innovation and medical progress.

Recent scientific advances in fields as diverse as genomics and nanotechnology hold out the promise of major therapeutic breakthroughs. Yet scientific discovery is moving much faster than the ability to translate those advances into real world products. We are failing, as a scientific community and as a nation, to adequately deliver the promise of science to diagnose, treat, prevent or cure disease. And a gap—some call it "the valley of death"—has formed between biomedical research and the development of new medical products.

We need to close that gap. And we can. But the solution is not to let companies make unproven claims about new approaches and new products.

The solution is to work together on a new set of flexible and modern standards of product review for the 21st century—through the emerging field of regulatory science.

Regulatory science involves the development and use of the knowledge and tools necessary for evaluating, ensuring and monitoring a product's safety, effectiveness, potency, quality and performance. We need regulatory science to develop new methods, assays, standards and models that will help speed the development, review and approval of medical products that patients need and can rely on.

The key is to build the strongest framework possible for this co-development … and mechanical engineers tell us the strongest shape is a triangle.

For regulatory science to have maximum effect on the drug development pipeline, we should not think of it as a pipeline at all. Instead of a linear progression from discovery to development to review and approval by the FDA, we should think of the process as a triangle—an Innovation Triangle—with three points—discovery science, industry and FDA—all coordinated in their efforts.

Rather than simply waiting at the end of the pipeline to approve or reject a product, FDA can help make trials more efficient by using qualifying biomarkers that accurately predict outcomes and by encouraging innovative trial designs that are equally effective but less burdensome and time-consuming.

Rather than accepting that the only way to test for drug safety is to expose cadres of patients to new products, FDA can help create innovative assays for safety that can better predict liver and kidney toxicity early on.

Rather than conducting its work in a black box, FDA can become more transparent and share key issues publicly, so that knowledge and insights can be shared and the field of drug discovery can move forward more quickly.

We must harness advances in science and technology to ensure that we have the most effective and efficient regulatory pathways to address the opportunities before us. And to do so, we must work together—academia, industry and government.

I should emphasize that regulatory science comprises an array of disciplines and approaches. Regulatory science takes place in laboratories, but it also involves clinical, epidemiologic, and statistical tools and information gathering systems.

Unlike work performed by specific sponsors, regulatory science is important for multiple products and stakeholders. The knowledge generated from such studies informs a whole body of innovation rather than a single product.

For example, promising research is underway using stem cells to restore brain function lost in patients with Parkinson’s disease and for use in other disease conditions. But before these treatments can reach patients, we must develop scientifically valid standards and manufacturing processes for stem cell therapies so they can be produced reliably and safely. Without these, the technology’s promise cannot be realized.

Basic research studies are identifying potential tumor markers that can indicate whether a patient’s cancer will respond to a specific therapy or combinations of therapies... whether there are subpopulations of responders or non-responders. But for these markers to be applied in clinical practice, ushering in the era of “personalized medicine,” the agency must use new science to identify subpopulations for treatment and to guide the evaluation and use of new diagnostic tests.

NIH, industry, and foundations are working together on an artificial pancreas for juvenile diabetes—which would continuously monitor a patient’s blood sugar and automatically

inject the right amount of insulin. But for patients to benefit, we must develop a scientifically solid testing path that ensures that the devices control blood sugar levels without risking hypoglycemia.

And we can defeat TB, a disease that has eluded us for centuries. NIH and others are supporting research into new, badly needed treatments for TB. But TB is complicated. It requires multiple drugs over many months to cure … and if you partially treat, drug resistance develops.

Fighting TB effectively requires combination products. But it will take forever if we have to approve each new drug independently and then look at how they work in combination. But that is how the process would traditionally unfold. Instead we have embarked on a new initiative to work with researchers and companies interested in developing combination products which will be reviewed as such. This is much more complicated for FDA scientifically, but it's what patients need and what public health demands.

These regulatory science challenges are not just for FDA alone. Regulatory science is a field of endeavor that must be embraced as an essential and dynamic component of our broader biomedical research enterprise. I urge you all to think about the science involved in the assessment of safety and effectiveness, and to engage in helping think through the next phase of scientific progress to support innovation in medicine.

To this end, I am especially pleased FDA has launched an important and broad collaboration in regulatory science with the National Institutes of Health—including the first ever joint funding announcement for regulatory science.

And, resources willing—we hope that through a competitive application process, FDA may be able to develop Centers of Excellence in Regulatory Science … which would support collaborative, targeted regulatory science research at academic institutions to address research gaps and priorities defined jointly with the FDA. These centers cold make a long-lasting difference, and they would be excellent training opportunities to help assure the next generation of work in this area.

I have to confess that I hadn't thought much about regulatory science until I arrived in my current position. But I recognize now, that some of my earliest thinking about these issues actually began here in Boston, during medical school, with the emergence of HIV/AIDS. I remember seeing these strange cases of immune deficiency, mainly in previously healthy young men; nobody knew then what the cause was and nobody knew what to call it.

But by the time I did my residency in New York City, I was taking care of lots of AIDS patients. But there was nothing we could give them. Patients were wasting away before our very eyes. There were no drugs available … only supportive care.

Soon thereafter, I worked with Dr. Anthony Fauci as assistant director of the National Institute of Allergy and Infectious Diseases. At that point in the AIDS epidemic,

candidate drugs were just becoming available. The great push was getting as many people as possible into clinical trials, so they'd have at least some chance for treatment.

Some advocates and others questioned why these clinical trials had to happen at all—they reasoned that patients facing death should have the chance to take anything that might bring them a benefit.

Not surprisingly, it turned out that some of those medications worked and others did not. Knowing which medications are effective has extended the lives of millions of patients in the United States and around the world.

And many of the key medications for HIV were approved in the United States first.

These effects were greatly served by early coordination between researchers, companies—and the FDA data requirements and clinical trial design. The introduction of new strategies using surrogate markers for effectiveness and novel clinical trial designs made the clinical studies easier to conduct.

There are many responsible for the tremendous advances in HIV care over the last quarter-century—including many I am sure in this room. Industry, academia, advocates … and the FDA—all played pivotal roles.

This is the kind of success we want to repeat and emulate for other diseases and conditions that take lives and cause disability. Indeed, this is the kind of success that FDA has helped make possible—repeatedly—over the last century, as we have incorporated new scientific standards into product reviews.

As we look to the new and emerging challenges of the 21st century, we require, now more than ever, an engaged academy, a strong FDA, and most of all—a recognition among each of us that, together, we can harness scientific progress for patients and for public health.

Thank you.