

**Remarks by
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Food and Drug Administration

"Modernizing Development Science to Unlock New Treatments"

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This text contains Dr. Gottlieb's prepared remarks. It should be used with the understanding that some material may have been added or deleted during actual delivery.

I want to begin with a story not from my work in Washington but from the front lines of ordinary medical practice. As some of you know, I still practice medicine. I work as a hospital-based doctor. It's a relatively new sub-specialty of Internal Medicine called "hospitalist medicine" or "intensivists."

As "hospitalists," we take care of patients admitted to the hospital's medical wards and cover the treatment of patients in the intensive care unit, in addition to admitting new patients to the hospital through the emergency room. By far, the most frequent reason for admission, and the most frequent medical problem I see on the hospital wards, is congestive heart failure, when the heart can't pump enough blood to the body's other organs. It's often the result of narrowed arteries that supply blood to the heart muscle -- coronary artery disease -- or from past heart attacks, with scar tissue that interferes with the heart muscle's normal work. What happens is that the lungs fill up with fluid that normally should be pumped away by the heart. Patients are sometimes left literally gasping for breath.

The treatments for heart failure are well understood. They include many old and some new medicines. And most work well. The problem is that diagnosing heart failure isn't always straightforward. The process is slow. It often involved a lot of trial and error. And it sometimes wasn't very precise.

But several years ago, I took some time off from the active practice of medicine -- less than a year in all -- to pursue policy work full time. In the year I was away from active medical practice, something remarkable happened. The diagnosis and treatment of heart failure changed. The entire process was not only made faster, but more precise, and safer, by the introduction of a simple process improvement. The introduction of a new test -- a biomarker -- that helped doctors quickly nail down the diagnosis -- a test called B-Type Natriuretic Peptide or "b-nat" for short.

B-nat can be easily measured in the blood. It is a substance secreted from the heart's ventricles in response to changes in pressure that occur when heart failure develops and worsens. The level increases when heart failure symptoms worsen, and decreases when the heart failure condition is stable. When the level is really high, it can be used as a measure of how wet the lungs are.

In the brief time that I took off from the active practice of medicine, everything changed about the diagnosis and treatment of one of the most common problems I saw in the hospital. Gone was trial and error approaches, the long time spent testing different medicines, or guessing at the diagnosis, trying to figure out if a patient had heart failure, pneumonia, or both.

A simple process improvement in the art of medicine, the introduction of a precise and well-validated biomarker, made the entire ordeal much more certain, much more precise, and much more safe.

I use this story only to make the point that it is possible to use new tools, new processes, as well as new biological markers, to make the practice of medicine and the art of diagnosis not only faster, but safer and more certain. And when you think about the drug development process, it is very much a similar practice. Drug development at its core, is about the practice of medicine. Which raises the question, can you use new markers, new approaches in drug development that allow that process to be made not only faster, but also safer, and more precise?

The answer of course is yes. We have seen it many times in drug development: where the introduction of a new test or a new approach allowed the entire process to be made more accurate, faster, and more precise.

We saw it for example with the introduction of viral load and CD4 counts as a surrogate marker for HIV or cholesterol as a marker for cardiac death or hemoglobin A-1C as a marker for the severity of diabetes.

And we are seeing it now with the introduction of markers such as progression-free survival and tumor shrinkage in cancer care as surrogates for survival and improvement in that disease.

We are also seeing it with the field of Toxicogenomics and the introduction of new sophisticated tests that can tease out toxicities to the heart or the liver or kidney much more quickly and with much more precision than the old methods -- methods which often involved waiting long times, and exposing lab animals and clinical trial patients to enough drugs until the organs were sufficiently diseased that they started to stop working.

I use this point to challenge a popular, yet wrong notion: that in drug development, speed and safety are opposing virtues. That every time we make process improvements in how drugs are developed that allow development times to shrink, to allow the process to be made more efficient and perhaps less expensive, that we are invariably making the process less safe.

This is not true. In fact, it is quite the opposite. Today too much of drug development is trial and error, and too often we fail to use modern scientific tools in drug development that could be giving us greater quantities of important safety and benefit information much sooner, and with more precision.

I am talking here about development time, not FDA review time, and the distinction is an important one. Review time is the time we spend evaluating applications. We have goals for how long we spend looking at applications, and we do a pretty good job of meeting them. But even while review time has shrunk, the total time that it takes to develop drugs has continued to increase, along with the total cost, because too many new drugs have to undergo multiple cycles of review by FDA or have to undergo testing and evaluation by methods that are sometimes needlessly slow, outdated, and in some cases simply obsolete.

When it comes to drug development, in too many cases, we're using tools to evaluate new drugs that were literally developed decades ago -- sometimes 50 years ago or more, to test and evaluate new medicines. We're using plain film x-rays to measure the response of cancerous tumors to new medicines even though tools such as functional PET scans might give us more precise information. We're using lab animals to test for common toxicities even though sophisticated panels of blood markers or "assays" might give us more information in less time. We're using empiric approaches to designing drug trials even though the mechanistic understanding of many new molecules is well understood, generating knowledge that could help us adapt clinical trials to yield more precise information about who is likely to benefit from a new medicine, and by how much.

The same kinds of scientific and process improvements that expand medical practice, making it more precise, more effective and safer can have the same benefits on the way we develop medicines. But modernizing our approach to drug development has not been one of our goals, until now. Too often, in the past, we settled for the tried and true ways of doing things, even if better scientific tools were available -- drug developers and FDA preferred familiar approaches.

That worked for a while when most of the medicines we were testing worked in similar ways, and were being aimed at similar ailments. But more and more, the new drugs that are being developed are based on completely new scientific approaches such as genomics and proteomics. More and more, new drugs are being targeted to very novel medical indications.

The result is that new medicines are increasingly bumping up against a scientific development process that isn't sufficiently advanced to evaluate them and move them to the bedside. We're not taking advantage of the same tools drug developers are using to discover new molecules to also test them for safety and effectiveness. So the entire process is not only too slow but it's outdated, and needlessly expensive.

We need to fix that if we're going to make sure that all of the discoveries that are being made in laboratories, all of the things you read about in the science section of the newspaper, are going to be made available to patients in the form of safe and effective new treatments. Despite many serious unmet needs for new medical treatments and significant investments in basic biomedical research, a new wave of medical products capable of saving and extending lives is not reaching patients or the FDA. The pace of new discoveries moving from the laboratory to clinical settings is not accelerating. The productivity of the medical product industry -- the sector responsible for turning new scientific discoveries into treatments -- is low and not improving.

It's clear that the product development process has become a bottle neck to medical progress. Despite advances in discovery of new molecules, a drug starting human trials in the year 2000 was no more likely to reach the market than one entering trials in 1985, roughly an eight percent chance. For drugs, the product failure rate in phase 3 trials has increased to nearly 50 percent. New product development science is needed break this bottleneck.

Without a focus and investment in the science of product development, we will not reap a full return on our nearly \$120 billion annual investment in biomedical discovery. We will not see the enormous investments being made by private industry, but the National Institutes, and by academic institutions, result in progress in the form of new and better medical products for patients.

And with so many people suffering right now from diseases that may be treatable or even cured in the near future, we can't wait many more years, and spend millions and even billions of dollars to develop each and every medicine, simply because our process for doing so isn't incorporating the most modern scientific tools and approaches and therefore takes too long and costs too much.

At FDA, we have recently set out two simultaneous efforts to confront these challenges. The first effort is to modernize the scientific tools we use to evaluate new drugs. And the second effort is to continue to make improvements in the process for regulating new medicines to make sure that we're incorporating the best management approaches, the best information technology, and the best quality systems and review processes to perform our daily mission.

To tackle the first challenge, under the leadership of Dr. Janet Woodcock, we have undertaken a new initiative to modernize the science of drug regulation as part of our Critical Path initiative.

Critical path is a broad initiative at FDA, involving all of our medical centers. The effort is aimed at catalyzing the creation of a new generation of scientific tools to enable product sponsors to better predict and evaluate the safety and effectiveness of candidate products; to make product development less risky and more efficient; and to enable individualization of therapy to improve effectiveness and avoid side effects.

Our goal is to translate the science developed under this initiative into FDA guidance to scientists and product manufacturers in order to clarify the regulatory path for modernizing approaches to bringing products to

market

Under Critical Path, we are working on long-term science development as well as near term improvements and modernizations in our own regulatory procedures to accommodate new scientific tools and approaches. For example, we are launching a clinical trial collaboration to validate the use of positron emission tomography imaging as a surrogate endpoint for cancer therapies, in partnership with the National Cancer Institute, the Centers for Medicaid and Medicare Services and other partners. We hope to expand this collaboration to include additional imaging technologies. We will soon be launching a new biomarker qualification program in collaboration with the National Institutes of Health. And we recently announced other new initiatives such as a framework for conducting early studies with micro doses, as well as a safe harbor for the submission of pharmacogenomics data, which we hope to soon extend to other kinds of data submissions such as proteomic data.

At the same time, we are developing regulatory guidance for incorporating these new scientific tools into the development process. One such guidance, which should be out in draft form this year, addresses how product developers can seek approval for a new drug and a diagnostic test for guiding the targeted use of that therapy, all within the same registration trial.

At the same time that we take steps to modernize the scientific tools that are used during drug development, we are also mindful to continue to take steps to modernize our own processes and approaches so that we are adopting modern management approaches and so that new scientific tools can become integrated into the registration process.

One way we can do this, for example, is to promulgate guidance on how scientists can use these new tools as part of the drug development process. We also want to continue to take steps to modernize our own internal approaches to evaluating the information we receive, and setting regulatory standards, whether it is through process improvements in our own work, through quality systems we adopt, or through technological improvements such as the incorporation of information technology to help us better evaluate the information we receive.

To these ends, I'm pleased to announce today a new commitment by the FDA to improve the process for collecting medical information as part of the so-called phase 4 trials or "post marketing commitments" drug developers often undertake after drugs are approved. Right now, sponsors often don't complete these important studies, sometimes they argue because the trials were too hard to enroll, or the clinical environment changed and the questions they were seeking to answer were no longer relevant to the practice of medicine.

We fully intend to work with sponsors to make sure these important commitments get completed. We have recently been evaluating more of these incomplete post market commitments at our advisory committee meetings. The cancer division recently had one such meeting, where they reviewed eight post-market trials that were never brought to completion. We want to take opportunities to evaluate these trials after they are set in motion to make sure they are still clinically relevant, and focused on finding out the most important information.

If there are improvements we can make in the design of these trials, or if the practice of medicine has changed in a way that the questions these trials seek to answer are no longer as relevant, we want to know about it and see how we can make the design of these studies more focused around the most practical and important medical questions that doctors and patients ought to have answers to in order to safely and most effectively use a new medicine.

Drug developers often argue that one problem that sometimes gets in the way of designing the best trials is that FDA often does not have the opportunity to discuss the design of these trials until very late in the drug review process, often weeks and sometimes even days before the agency is expected to make a final decision to approve a new drug. So there isn't a lot of time for careful scientific discussion between FDA and drug developers about how to design optimal trials. With more scientific exchange, it may be possible to design better trials that will answer important questions with more accuracy and more certainty.

So I am pleased to let you know today that FDA is in the process of undertaking the first step in an effort to evaluate and perhaps improve how post marketing commitments are developed and implemented by the agency, and how we work collaboratively with scientists and drug developers to design optimal studies and to make sure they are brought to completion after new drugs are approved.

To begin, we will be contracting with an outside group to undertake a thorough evaluation of how these commitments get designed and implemented. We are currently negotiating the contract to undertake that study and should be ready to announce it in a few weeks. The objectives of this effort are to evaluate the consistency of the processes within divisions, across divisions, and across the different medical Centers at FDA for requiring, requesting, facilitating, and reviewing post market commitments. We want to identify any obstacles that may result in these processes being less efficient or consistent than they ought to be.

Additional objectives include recommendations for and assistance with implementation of standard policy and procedures for requesting post marketing commitments which reflect FDA's best practices, and creation of a quality system for justifying, drafting, and reviewing post marketing commitments. This will include additional training for reviewers and management on the best way to design and implement post marketing commitments.

This contract is not intended to assess the tracking and monitoring systems for post marketing commitments. Instead, it is intended primarily to identify and improve the scientific decision-making process around the design of these important studies. Once the contract is announced in the next few weeks, the evaluation is expected to take a full year. We believe the results of this analysis will lead to recommendations for how we can improve the process for designing and implementing post marketing commitments.

These studies are a vital part of evaluating the safety and effectiveness of new drugs as well as new devices. Even the largest and best designed pre-market studies cannot reasonably answer all of the important questions patients and doctors have about medicines. No reasonably sized clinical study can evaluate all of the subtle effects of medicines, including new indications for a medicine or the very rare side effects that may occur only once in tens of thousands of patients. Continuing to evaluate drugs after they are approved -- in post marketing trials as well as the routine collection of bottom line information from ordinary medical encounters -- is an important part of ensuring their safety and learning new things about their benefits.

These are just a few examples, I spoke about today, of how we want to use modern science and improvements in our own process at FDA to make sure that we're using the best tools and best approaches to determining the safety and effectiveness of new medical products, and that we're doing all of these things in an efficient way. The bottom line is this: There are many opportunities to improve our current process for drug development -- improvements that could shrink development times -- not review times, but total development times -- and even more important, improve our ability to determine the safety and effectiveness of a new medicine much earlier, and perhaps with less cost.

Working together, by harnessing modern scientific tools and smarter approaches to our work, we can improve the development process, making it more efficient -- yes faster -- and more effective at demonstrating safety and effectiveness, so that innovative new medicines can get to the patients who need them.