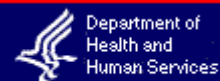




**U.S. Food and Drug Administration**



**CENTER FOR BIOLOGICS EVALUATION AND RESEARCH**

**Speech before**

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University of Georgia College of Pharmacy

**Remarks by**

Scott Gottlieb, MD  
Deputy Commissioner for Medical and Scientific Affairs  
Food and Drug Administration

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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.*

Thank you for the opportunity to speak here today. I want to start today by thanking Gary Dykstra and his team for helping to organize this important annual event, and the University Of Georgia College Of Pharmacy for their collaboration with FDA and their work to advance the public health.

This kind of scientific collaboration is more important than ever if we're going to make the most of recent advances in medicine and life sciences. All you have to do is look at the opportunities being offered by many of the medical technologies just now making their way to patients, or in the pipeline, to understand why we constantly need to be challenging ourselves here at the FDA and in the broader scientific community.

Drugs already developed have brought tremendous benefits: preventing hospitalizations, eliminating surgeries, or getting a patient out of an institution. And even more important are the benefits of these medicines in terms of saved lives, reduced suffering, and more productive and fulfilling lives.

The Centers for Disease Control reported again recently on continuing improvements in mortality rates from heart disease. Fifty years ago, physicians had few strategies for managing heart disease. Today they have stents and angioplasty to open clogged arteries; beta-blockers and calcium channel blockers to lower blood pressure; and statins and aspirin to prevent heart attacks. David Cutler, an economist at Harvard University, has estimated that today the average 45-year-old can look forward to about three extra years of life thanks to improvements in heart disease treatment.

Last year, the National Cancer Institute reported that, from 1993-2002, mortality rates from all cancers combined fell by 1.1 percent per year. Mortality rates also fell for 12 of the top 15 cancers in men, and nine of the top 15 cancers in women. Cancers that a few decades ago were certain death sentences are today being treated as chronic illnesses or even cured. The same progress can be seen in other fields of medicine.

And so for all of these reasons, and many more, we need to make sure we are getting safe and effective new medical technologies to patients as quickly as we can.

While healthcare achievements in past decades have been impressive, recent progress in genomics, proteomics, information technology, and many other fields of science and medicine should promise even greater improvements in our lives in the years ahead.

We achieved the improvements in cancer and heart disease and other diseases during the past few decades without the sophisticated science of genomics – the human genome was sequenced in just the last several years. And now genomically-based drugs, and cell and protein-based therapies based on genomic sciences, are making up a growing number of the new drugs entering early stage clinical trials.

We also achieved our recent progress without the new science of proteomics, and an increasingly sophisticated understanding of how gene and protein expression interact to cause disease in individual patients. In a burgeoning field referred to as systems biology, scientists are using information technology to exhaustively study the genome and proteome to look at the big picture of biology and disease – examining ways in which they are integrated and interact within a particular organism or function.

And we achieved our recent gains in health without a new generation of increasingly powerful biomedical tools based on the latest information technology that can enable sophisticated systems for collecting and evaluating clinical data and supporting effective medical decision-making. These additional tools increase the future potential for even more effective, more targeted, and perhaps more individualized medical treatments that can cure or at least slow or halt disease progression.

I believe, owing to these scientific advances, and many others, there is a lot of medical progress that were poised to realize in the next decade or two. This progress may dwarf the recent gains we've seen in disease and health and it may already be showing up at FDA, in the way of many more early applications for innovative molecules being filed with the agency as part of investigational new drug applications.

These applications mark the first time that drug developers come to FDA to get permission to begin testing their new molecules in people, as part of the typical three phases of clinical trials. And many of the INDs we're seeing are for molecules developed with many of these new scientific tools. Moreover, the amount of work sponsors are doing for each of these IND applications, the number of meetings they ask for with FDA, is also increasing a lot. We think this increased intensity of work around these early applications may reflect the increasing complexity of the molecules themselves as well as the more difficult medical indications that sponsors are targeting.

Now complexity is a crude proxy for measuring just how beneficial these new drugs might eventually be to patients if they make it through the development process and are demonstrated to be safe and effective. But if more of the drugs being put into development are based on very novel mechanisms and if more of the drugs are targeting new or very difficult medical indications for which there aren't a lot of available treatments, that holds out the promise that tomorrow's medicines may offer a lot of different opportunities for patients than the medicines available today.

But with so many people suffering from diseases today that could be more treatable or even cured in the near future, these new molecules are still taking too long to be turned into practical solutions patients can safely use, and scientific breakthroughs aren't resulting in medical benefits soon enough. And too many are failing late in the development process, after we have already sunk in a lot of time and money and exposed many patients to experimental treatments. The plain truth is that despite all of our scientific progress in recent decades, the chances that a new molecule will be successfully developed into a safe and effective medicine hasn't changed one bit, even while our investments in research have grown enormously and the cost of developing medicines, by some estimates, has nearly tripled in just the last decade.

This isn't a recipe for success as a healthcare system. As health care costs continue to rise, it's increasingly important to make sure we are taking steps to address concerns about making sure those new medical innovations that can help end suffering and reduce overall healthcare costs are not themselves priced out of development. And we need to make sure that all of the enormous investments we're making in research start to pay off in the form of many more new and better medicines. By some estimates total R&D spending, once you factor in the money spent by the National Institutes of Health as well as private companies and public institutions, tops \$120 billion a year. That's a lot of spending, and we need to make sure we're getting the most from it. We've seen a lot of basic science discoveries made in laboratories in recent years, and

it's surely a result of those investments in research. But when are we going to see these basic discoveries turned into practical treatments that can help patients suffering from too many diseases.

The problem is that too many of these basic science discoveries are become mired in a development process that is too slow, too costly, and not sufficiently advanced to properly evaluate all of the sophisticated molecules being discovered in the laboratories. The plain truth is that all of that terrific, highly advanced science that we've developed in the last few decades is not resulting in highly innovative new molecules. But once those molecules leave their sophisticated laboratories, they enter a development process where the scientific tools have often been stuck in time for decades or more.

I believe this is a big reason why we're not seeing all the progress we expected from the enormous investments we've made in basic science. It's one of the reasons medicine is so costly, and better treatments that are significantly more effective than older generations of medicines seem so hard to come by.

It doesn't need to be this way. Right now, the way that we're approaching drug development is the exact opposite of what has happened in other high technology fields in recent years. In other fields, the tools for developing finished products have undergone dramatic advances, resulting in better products being turned out faster and at a lower cost. Look what has happened to the design of airplanes or even microchips, where advances in the development process itself are largely responsible for the dramatic advances in the finished products that are produced.

But none of this is true when it comes to drug discovery. In drug discovery, the best ideas still bump up against some of the oldest development tools. In drug discovery, all of the work and investment and innovation have gone into the front end, the discovery side of science. Little or no attention has been paid to the middle part of the process, the development part, when drugs are tested and manufactured and turned into medicines.

This is a big reason why we're not seeing many more medicines and why costs keep going up and development times continue to increase. The result is all of that good science that we're developing at the front end of the discovery process is not coming out the other side in the form of better drugs. All of that science is getting squandered in the middle, bogged down in a development process that is out of date.

Achieving these goals - moving from a "proof of concept" with a new molecule discovered during a basic biomedical research program to giving doctors and patients confidence about the value of that treatment in actual care requires solving countless hard problems, particularly for the many unique technologies under development today and the many small and innovative, but inexperienced companies that are starting up this effort. We need to do something about this critical public health challenge in order for patients to get access to the many potentially valuable new treatments that are at early stages in the pipeline now, in a timely way and at an affordable cost.

The FDA needs to help improve this process because the developers of new drugs have one bottom line in mind as they move new molecules through the development process: getting FDA approval. This is true of everyone involved, from generic drug companies to large pharmaceutical companies to biotechnology concerns. Large companies have developed "quality systems" or programs that focus their management efforts on this bottom line. Small companies hire consultants and struggle to put together research programs that can result in applications that meet FDA standards.

But big or small, if the pathway isn't clear about how to do that, or if the pathway doesn't take full advantage of drug development technologies that could accelerate and improve the development process, or if the research that would improve the translation of basic science into new medical products is not well supported, and finally, if product developers or scientists engaged in the development of new drugs are not able to take advantage of the knowledge base at FDA, then the pathway to developing a safe and effective product will be longer and harder and more uncertain than it needs to be.

Addressing all of these challenges – the need for better, less costly development and manufacturing pathways for safe and effective new drugs -- is going to require a broad effort on the part of the pharmaceutical and biotechnology industry, academic researchers, researchers at the National Institutes and other government research institutes, and finally the FDA.

The FDA is trying to do its part. We are the world's gold standard for safety and effectiveness, and we intend to do all we can to keep it that way. We have expertise in these determinations because of our substantial experience in all areas of new medical product development. Through the applications that are submitted to the FDA and the questions our medical review staff are engaged in answer on a daily basis, we have amassed what is potentially the most valuable knowledge base for

identifying the benefits and risks of new treatments in the world from all the data that have been and are being used to support product applications.

At FDA we've taken a number of steps in recent years to address this problem and bridge the development divide. You've probably already heard a lot about our critical path initiative, being led by Janet Woodcock, FDA's Chief Operating Officer. Our critical path initiative is aimed at improving the scientific tools we use to evaluate drugs in clinical trials. Soon, we're going to be releasing our critical path opportunities list which will highlight areas where we think better scientific tools can continue to improve the way that new drugs are tested. Our opportunities list will focus on many areas, but two in particular: new scientific projects for improving the way clinical trials are designed, and the opportunities to validate better measures for toxicity and efficacy of medicines.

Today I want to talk about another part of the development process, the manufacturing process, and steps we're taking to modernize the science of this part of the process. Like clinical development – manufacturing has also become a bottleneck in recent years to getting medicines to patients. Too often, drugs are delayed from the market because of manufacturing problems, or new tools that can improve the process while reducing the cost of manufacturing the drugs go underutilized. Like clinical development, manufacturing hasn't benefited in recent years from the same kind of scientific advances that have helped advance other industries, or even advances that have become part of the front end of drug discovery. That needs to change if we're going to realize all of the potential from those new discoveries that are being made in laboratories, and if we're going to help reduce the cost of getting these treatments to patients.

As we begin to see more novel drug delivery systems and complex drugs, addressing key quality issues and establishing meaningful specifications become important. There's a need to better understand the relationship between quality and safety and efficacy and to apply risk-based approaches for establishing relevant quality specifications.

Conventional drug manufacturing is generally accomplished using batch processing with in-process and final product testing conducted on samples to assure quality. This approach has been successful in providing quality drugs, but there are still important opportunities for improvements in the efficiency and quality assurance by better and more innovative applications of modern process development and control technologies including modern process analytical methods.

The problem has been that the drug industry seemed hesitant to introduce these new techniques and technologies. And from a public health perspective, this is undesirable. One reason often suggested for this hesitation is "regulatory uncertainty" -- in some instances, people didn't know what to expect from the FDA.

The truth is there are important regulatory and technical questions that need to be addressed. But our GMP regulations for drugs haven't been updated in 25 years. Meanwhile, best practices in manufacturing technologies and methods have undergone significant progress over that time, particularly in other high-tech industries.

For example, the semiconductor industry like the drug industry also has a very low tolerance for impurities and inaccuracies in production. And when its production processes were lagging because of high costs and too many errors that industry helped invent the "six sigma" production methods. Through continuous quality improvement, those methods achieved enormous improvements in production cost and quality, and they have since been widely adopted in manufacturing industries.

But manufacturing hasn't received its due attention in the pharmaceutical industry, even though many experts on manufacturing processes including many of you here today believe that large savings in production costs could be realized while achieving even higher quality standards. That needs to change. And we need to make sure that our regulations are encouraging and facilitating such progress, which is needed today more than ever.

So our broad-based GMP program is aimed at developing new regulatory policies based on the latest science of risk management and quality assurance. The new standards are being designed to encourage cost-reducing and precision-enhancing innovation in manufacturing and technology, and to ensure that all three FDA medical centers use consistent and up-to-date methods, including inspectors specializing in particular types of production methods.

Drug manufacturing is evolving from an art form to one that is now science and engineering based. Effectively using this knowledge in regulatory decisions and in establishing quality specifications we all use, and then finding better ways to

evaluate manufacturing processes -- this can all significantly improve the efficiency of both your manufacturing programs and our regulatory processes.

The initiative that we've been working on together is designed to do just that through an integrated systems approach to product quality regulation. And so in this regard, our model for a good manufacturing program can be characterized by one where:

Product quality and performance would be achieved and assured by design of effective and efficient manufacturing processes;

Where product specifications would be based on mechanistic understanding of how formulation and process factors impact product performance;

Where there would be continuous "real time" assurance of quality, and continuous quality improvement;

Where regulatory policies and procedures would be tailored to recognize the level of scientific knowledge supporting product applications, process validation, and process capability, and;

Where risk based regulatory scrutiny would relate to the level of scientific understanding of how formulation and manufacturing process factors affect product quality and performance and the capability of various strategies to prevent or mitigate the risk of producing poor quality products.

Our efforts to achieve these goals through our GMP initiative are founded on sound science and engineering principles for how we can better assess and mitigate the risks of poor product and process quality. I know that many of you have been instrumental in helping us understand and begin to meet these challenges. At FDA, we appreciate these scientific collaborations, but we also know that much work still remains.

Through our policies known as "current Good Manufacturing Practices" or cGMP initiative, under the leadership of Janet Woodcock and David Horowitz and Joe Famulare and many others, FDA has set out to overhaul our regulatory and quality control systems for pharmaceutical products, to encourage manufacturers to modernize their methods, equipment and facilities, to lower costs as well as improve the quality and reduce manufacturing glitches that sometimes keep drugs from the market.

As you recall, in August 2002, we announced the Pharmaceutical Current Good Manufacturing Practices (cGMPs) for the 21st Century initiative, to enhance and modernize the regulation of pharmaceutical manufacturing and product quality — to bring a 21st century focus to this critical FDA responsibility.

This initiative intends to modernize FDA's regulation of pharmaceutical quality for veterinary and human drugs and select human biological products such as vaccines. As part of this initiative, the inspection, as well as the chemistry, manufacturing, and controls (CMC) regulatory programs were evaluated to develop a modern and integrated pharmaceutical quality regulatory system

A key element of the cGMP initiative is our effort to encourage adoption of state-of-the-art quality control systems in manufacturing. This work is based on a premise that has guided improvements in manufacturing processes in other industries. That quality cannot be tested into products; it should be built into products by design.

This includes the use of process analytic technology, for design, analysis, and control of manufacturing, with the goal of ensuring final product quality by allowing timely measures, during manufacturing, of critical quality and performance attributes of raw and in-process materials.

We are also identifying key applied science questions that are part of the submissions that companies make to FDA that need to be addressed, and working to address them.

This includes changes in how we approach the CMC portion of drug submissions, to make sure that the focus is on critical understanding of the manufacturing process itself and less on format and data.

Under the leadership of Moheb Nasr, the head of FDA's Office of New Drug Quality Assessment (ONDQA), the agency is developing a new pharmaceutical quality assessment system based on scientific knowledge and understanding of product and process that applies quality-by-design principles (QbD). The objective of QbD is to facilitate innovation in product and process development and continuous manufacturing improvement throughout product lifecycles.

We want to provide regulatory flexibility to set appropriate specifications and incorporate post-approval changes that can lead to better outcomes, and we want to streamline the submission and the review process to help make the adoption of better technologies and approaches to manufacturing more efficient and less costly.

A manufacturing plan developed under a quality-by-design approach enables the product design to meet patient requirements right from the start. The attributes of the raw materials and process parameters are linked to product attributes. Quality by design allows the impact of product attributes and patient safety and efficacy are well understood, so as changes are introduced to improve efficiency, it can be quickly and clearly determined whether or not the goal of improving quality without negatively impacting safety and efficacy can be achieved.

To accelerate these developments and the QbD approach for CMC submissions, we recently restructured the CMC office, and also added additional engineers and pharmaceutical scientists to its staff.

Last fall (October 5-7, 2005), we co-sponsored a workshop to try and develop an internationally harmonized approach to quality by design. We're also working to develop an ICH guideline on comprehensive overall quality summary and eventually will articulate our approach to encouraging adoption of QbD in a guidance document. We also plan to issue our Quality Systems final Guidance by the summer of 2006.

The CMC staff is working in close collaboration with the pharmaceutical inspectorate staff in the field, who are also adapting their scientific approaches and their tools to better target their critical inspectional work on areas of manufacturing where the greatest risks are found as well as the best opportunities for measuring quality approaches. It's important that we are taking an efficient, risk-based approach to how we inspect facilities, to make sure we're getting the most regulatory bang for our buck and identifying the areas where problems are likely to lurk.

To help achieve these ends, we also plan to complete soon a report that summarizes the work of our risk management work group, which was charged with identifying continuous improvements in the risk model for prioritizing sites for manufacturing inspections.

Developing and manufacturing new medical innovations is a difficult and complex process, but one that can bring great value to patients. I'm confident that the same collaboration and innovative thinking that your bringing to the FDA to help us tackle some of our challenges on the manufacturing front can also be brought to bear on other pressing challenges in our regulatory mission.

We also need to remember that the long and difficult process of improving the process for developing and manufacturing new drugs is a delicate one that requires the right mix of incentives, safeguards, and effective regulation to make sure people can derive the maximum benefit from safe and effective new medical technologies. Only by adopting policies that improve the process for developing new medical technologies while protecting the incentives to develop new innovations and reward cost-effective medical practice and the most high value use of new technology, will we continue to realize the full public health benefits of these innovations. We look forward to working with all of you on these shared goals and appreciate your participation here today.