

Bringing Home the Genome: the FDA's Role in Realizing Personalized Medicine

Margaret Hamburg, M.D., FDA Commissioner

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I'd like to thank the Personalized Medicine Coalition for inviting me to address your luncheon today. I admire the energy and ingenuity your group has shown in working to support the realization of the potential of personalized medicine and in fighting to keep the issue of personalized medicine at the forefront of discussions about healthcare reform and biomedical research.

You understand, as do I, that tailoring medicine such that the right therapies are delivered to the right people is likely to be one of the most important themes for healthcare of the future.

The concept of personalized medicine is the understanding that people differ in their genetic makeup, their environment and their lifestyle and that these differences are critical factors in the severity and type of disease and how individuals respond to therapies.

But as I have been learning, the term "personalized medicine" can mean many different things... from the development of foods that are customized to work with your own metabolism, to the creation of a personal map that can chart a course to avoid inherited disease, to the prospect of health care savings driven by a knowledge of which interventions are most effective for the greatest number of people.

The concept of personalized medicine is really broad enough to encompass many different activities at the Food and Drug Administration...

For example, we have just launched a new radiation safety initiative, which is aimed at reducing overexposure from imaging devices for example, by giving patients a medical imaging record card so they can personally track their exposures. This is an important form of personalized medicine...

But I think that we are all here today to talk about personalized medicine in the context of the application of genomics in the development and use of drugs and other therapeutics.

The development of such new medical products depends, of course, on advances in science. Getting these therapies to people depends on the FDA—the regulatory agency that will render a decision on whether a new product will make it to the market.

As a science-based, science-led regulatory agency, the FDA must respond to the extraordinary advances in new science and technology which offer great opportunities, but also challenges to our capacity for research, development and regulatory processes.

As we endeavor to translate the great promise of new science and technology into real-world products for those who need them, it is essential that we have a regulatory agency that is scientifically robust and trusted by policy makers and the American people.

We must be able to understand, respond and contribute to the full range of innovative new products that will come before us, and we must leverage advances in science and technology to ensure that our regulatory systems are as effective and efficient as they can possibly be.

Just as biomedical research has evolved in the past decade, regulatory science – the science and tools we use to assess and evaluate a product's safety, effectiveness, potency, quality and performance – must also evolve.

Our regulatory scientists must be able to understand therapies that are being developed using the most recent scientific advances. They must have the right tools to evaluate these therapies. And they must be a partner to the greater scientific community as they work to bring these therapies to patients.

And I want to underscore the point that we are all in this together.

Our nation has invested billions of dollars in biomedical research – an effort that is indispensable for medical progress – but this research will not result in cures unless it is married to a robust investment in regulatory science. ...and to modernizing the FDA's regulatory capacity.

In this context, I'm proud to note that yesterday, Secretary Sebelius and I, along with Dr. Collins of NIH, announced a first-of-its-kind collaboration between NIH and FDA. We have established a Joint Leadership Council to enable our agencies to work together to improve regulatory science—beginning with a program of grants to advance important research in regulatory science.

A robust, state-of-the-art field of regulatory science is essential to FDA's work. But more than that, it represents an important driver of our nation's health, the health of our health care industry, and the health of our economy.

The first decade of the 21st century began with the decoding of the human genome—a scientific achievement that we knew had the potential to transform our understanding of health and disease and revolutionize our fundamental approach to medicine.

We understood that this breakthrough would lead to the development of new and better therapies and the ability to more finely attenuate risk and benefit...if not for every single patient, at least for patients in particular, identifiable patient sub-populations.

But as you know, this isn't happening as fast as we would like. In the few short years since we cracked the human genetic code, we've come to understand that while that scientific achievement was revolutionary in nature, our path toward realizing all of its potential for medical treatment is evolutionary...progress forward is real, but incremental, and very often, much slower than we might have wanted.

In part, this is due to the complexity of the human organism. At the dawn of the genome age, some were predicting that once we'd identified the genes, we'd have targets that we could easily alter with new drugs, curing one disease after another.

No doubt we will develop more sophisticated strategies based on our growing understanding of our genetic make-ups.

But I don't have to tell you that for now, at least in many cases, identifying genes that seem to be linked with a disease is only the beginning of an arduous process. New approaches to the drug development paradigm are needed such that new drugs are developed along with the tests that inform their use. New designs for clinical trials are needed so that genetics or other markers can be used to assist in patient selection. And both clinicians and patients need to be educated so that we can actually see personalized medicine move from concept to practice.

As a foundation to this all, we must ensure that the FDA has the scientific knowledge, tools, and standards needed to regulate these novel products—often combination products. This is an important component of our new initiative in regulatory science.

Like you, FDA would like to see personalized medicine as an approach that will not only help patients get better treatment, but one that will reduce healthcare costs.

Clearly, we can have much better outcomes for patients if we can discern what distinguishes one group from another, in terms of both positive and negative responses, and design a clinical trial based on that knowledge.

And we have examples of where this has worked.

One important instance is where knowledge about the genetics of drug metabolism has been applied to evaluating responses to the blood thinner warfarin, a vitally important drug, yet one that causes more adverse events than almost any other. FDA approved a label change in 2007 to list genetic tests relevant to the dosage of warfarin, and earlier this month we approved another change that gives doctors guidance as to how to match genetic test results to particular initial doses.

The metabolism of warfarin is complex, and further refinements no doubt await us. But FDA's work on this drug constitutes an important step forward in making it easier for clinical practitioners to take advantage of genetic information. With the knowledge provided by FDA scientists, doctors stand a better chance of finding a dose of warfarin that is safer, with fewer hospitalizations, other costs and trauma for the patient.

We can also apply pharmacogenetics to our understanding of who are the patients who should and should not receive a drug, period. Sometimes, perfectly good drugs may harm patients with certain genotypes, but there are promising examples of being able to identify patients at risk for serious adverse consequences from use of a particular drug or class of drugs, and exclude them from the treatment population. In one case, the HIV drug Abacavir showed very good response rates for many patients, but a relative few patients suffered severe adverse reactions which included fever, gastrointestinal and respiratory distress. Once we could identify the at-risk patient population by the presence of a genetic variant called HLA-B 5701, we could seek to exclude them from the patient population. The drug label now carries the warning that patients with this variant are at risk for severe adverse reactions. Clinicians can now prescribe the drug for their patients with confidence following a test for that genetic variant.

Sometimes, genetic markers can inform us about expected benefits from certain interventions. For example, the label for 2 FDA-approved colon cancer drugs now contain the recommendation that patients should be tested for the presence of the K-RAS mutation before starting therapy, because we now know that patients with that genetic mutation are highly unlikely to see a positive response from those therapies.

This is important, because when patients are battling cancer they don't have time for trial and error; prescribing an ineffective course of treatment wastes precious time in the fight against a potentially fatal disease progression, and the toxicity from exposure to an ineffective therapy can undermine their efforts.

FDA's Office of Clinical Pharmacology is currently looking at data that shows that genotyping can help doctors who are considering whether to treat childhood leukemias with cisplatin. When a child has one of two genetic alleles, doctors can vary the dose, or use another drug, and thus stand a better chance of protecting their young patients from suffering devastating hearing loss.

In order for the FDA to build on the promise that personalized medicine holds for new and better therapies,” in addition to our roles as “reviewer” and “regulator”, FDA must also serve as a “catalyst” for innovation.

This involves, among other things, increased outreach and collaboration with industry, academia and our government research colleagues.

For example, FDA’s Center for Drug Evaluation recognized early on that in order for companies to make a serious investment in genomics, they had to believe that FDA was serious about the science and learning how to incorporate it into the medical product review process. In 2003, the center established a Voluntary Data Exchange program and asked companies to voluntarily submit to the agency genomic data which they had collected in the drug development process.

It was a slow start; companies had many understandable concerns about submitting additional data to the FDA, outside of an official drug review. They were afraid that the agency would act prematurely on the data, create more work for the companies, or create obstacles to drug development. It took a few years for the agency to allay those fears.

But today, FDA’s Voluntary Data Exchange program has dozens of submissions from developer companies and there have been several meetings that enable FDA reviewers to learn about the technology in order to understand how to apply it in the review process while enabling developer companies to gain critical feedback from reviewers about how to structure the data in a new drug application.

And perhaps most encouraging for patients, these voluntary submissions are now moving into actual new drug applications so that advances in genomics can be utilized in new therapies.

With a consortium of academic and industry scientists working within our Critical Path Initiative, we’ve worked to validate new biomarkers in drug discovery. So far we’ve agreed upon the use of seven rodent assays that can be used to pick up early signs of kidney toxicity.

We expect that the biomarkers area will get an important boost in the next few months when we issue draft process guidance on biomarker qualification. This will enable developers to gain a clear picture of the criteria the FDA will use to vet the usefulness of biomarkers in the evaluation of clinical trial data.

For the agency, genomics represents a challenge, as well as a unique opportunity, to integrate some key review functions. As most of you probably know, within the FDA there is one center that evaluates drugs and another one that evaluates medical devices.

As determined by statute, the regulatory approach to granting pre-market approval for drugs and biologics is different from the one which applies to medical devices. But personalized medicine in the treatment of disease requires the integration of drugs and diagnostics.

As Commissioner, it is clear to me that we need to develop a consistent, comprehensive and integrated approach to the evaluation and regulation of medical products which separately, and in combination, comprise the practice of personalized medicine.

We know that for developers to make a substantial investment in this still-evolving arena they need clear guidelines setting out our expectations and approval standards.

There are many components to getting through the regulatory process for co-development of drugs and devices, and we intend to work on all of them. We intend to clarify our expectations

for the kinds of clinical trials and levels of confidence needed to satisfy us that a test is accurate and that it can be used to help shape clinical judgments. As an integral part of this process, we also are working internally to make sure we have a common understanding across all centers and throughout the agency about the kind of evidence needed when a test result is being used to shape a drug trial, or drug approval or relabeling. We also intend to make sure the communication lines between sponsors and CDER and CDRH are clear, and that sponsors get consistent advice about how to take the next step in development.

We expect to have this guidance finished by the end of the year.

There is also room for us at FDA to focus on the important discoveries to be made by mining the information we already have. FDA has a vast storehouse of data from past trials. Looking forward, new biomarkers which can identify the patient sub-populations most likely to have a positive response or an adverse reaction to a drug, could be applied to applications that never made it through the FDA review process.

By viewing the data from unsuccessful past trials through the lens of new biomarkers, it may be possible to turn past failures into future successes. And, as I've touched on today, there are already many compelling examples of how new diagnostics are being applied to drugs and biologics that are already on the market, resulting in enhanced safety and effectiveness for patients. Using data and samples from past trials may also help us design better trials in the future

There is a lot to be done.

As FDA Commissioner, one of my priorities is building on the strong foundation already established by the professional staff in our Centers for Drug Evaluation, Devices and Biologics. And while I don't yet have a specific answer to the question "how do we accelerate our path to the future and its potential", I do know that the approach we take now will determine our way forward.

Regulatory agencies are not known for being *flexible*... but that is exactly what we need to be.

At FDA, this starts with the recognition that incorporating genomics into medical product review requires an interagency, multi-disciplinary effort that transcends the boundaries of any existing center. In order to be truly effective, we need to develop a regulatory framework that reflects the task ahead.

Regulatory agencies are not known for being *collaborative*... but that is exactly what we need to be.

At FDA, this means increasing efforts to reach out to industry in order to identify existing obstacles to innovation and, together, finding ways to maneuver around them. It means working in partnership with our government colleagues in research, oversight, enforcement and other key areas to identify knowledge gaps and fill them; identify confidence deficits and address them.

Regulatory agencies are not known for their *openness* and FDA, in particular, has gained a reputation for being a bureaucracy-bound "black box." We must be more transparent and endeavor to help the public understand the rationale and reasoning behind the decisions we make which have such far-reaching impacts on public health.

Regulatory agencies are not known for being *clear*, but that is exactly what we need to be.

Just as few runners would show up for a race without knowing the distance to the finish line, medical product companies will not make large scale investments in the science and technology that can lead to safer and more effective therapies, until they know what we will require of them in the review process.

Through voluntary data exchange, published guidance, regulation, and every other method of communication available to us, we will establish a clear and illuminated regulatory pathway to product approval.

This all sounds very ambitious, I know.

But biology—and the very foundation of genomics—teaches us that successful organisms *are* successful because they do one thing very well: they adapt.

At the dawn of the atomic age, Albert Einstein said, “everything has changed except for our way of thinking.” In these, the early days of the *genomic* age, we are trying to adapt our thinking, our regulatory system, our models of drugs development, research, clinical trials and the very way we look at, gather and analyze data ...to a new reality.

The process of shifting paradigms and creating new models is not easy. But I’m sure that the reason that most of you are here today is that you are excited about the opportunity to be involved in the process of helping to transform the way we think about genomics and its application to the discovery of new medical therapies, in these still early days.

There are many challenges before us, but I believe that a future that provides safer and more effective therapies for all of us is well worth the effort.

I look forward to working with your group and others to bring this about.