Critical Path Initiative and FDA's Vision for Personalized Medicine
Janet Woodcock, M.D.

DR. WOODCOCK: Good morning. Can everyone hear me? Okay. Good.

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I'm really happy to be able to be here and talk about our Critical Path Initiative because it really is in many ways closely linked to genetics and to pharmacogenetics, and these two things, although they're not exclusively the same, have a lot of connection.

I was asked to talk about the Critical Path Initiative with particular emphasis on personalized medicine and I think that's because the genetic part of this really does pertain to personalized medicine.

So first I'm going to walk you through some of the background quickly on how FDA got to have this initiative and what the issues from our point of view are.

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Of course, I'm sure this committee has discussed in great length all the unmet medical needs that exist in our society and the fact that for biomedical discovery this is really a golden age and it isn't just the sequencing of the human genome but a huge variety of additional technological and scientific advances that have led to the generation of thousands, literally, of new targets within the body, new pathways. At the same time for medical devices for really unprecedented ways of investigating in the gene and intervening in the body mechanically or physically. So we have this tremendous burst of creativity and information at the discovery science level.

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In addition, recently published in JAMA the ten year investment in biomedical research has doubled over the prior decade in real dollars so our economy is continuing to pump investment into the biomedical R&D sector. Most of that in industrial, 57 percent, but quite a bit from the government, federal government, and some even state governments increasingly. And increasingly even from private sources such as Gates Foundation. So there has been a huge serge of investment at the same time that the biomedical science is really exploding.

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And this just shows a couple of trends of pharmaceutical R&D spending over the '93-2003, as well as the NIH budget. You can see the increases are somewhat parallel and this is reflected in other sectors, although it's not as easy to get the numbers.

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And everybody, the public and so forth, has been expecting a matching acceleration in products coming out the other end. I'm sure the insurers have been bracing themselves for this.

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This is what we see. This is the ten year trends in drug and biological submissions to the FDA. So this is not to say these are—the FDA is turning a lot of things down. This is what FDA gets in the door. Over the same decade I've arrayed the submission rate over the same decade I showed the investment. You can argue whether this is going down or is flat but we can all be in agreement this is not increasing. The submission rate is not increasing. This is biological products and drugs.

Devices look a little bit better in innovation but certainly not exploding. It's harder to array the device numbers in a reasonable way because they're so disparate.

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So this has been various called by people the pipeline problem or industry productivity problem or some kind of problem or whatever but, in fact, we're not seeing a matching acceleration in innovative new products coming to market that we would expect from this level of investment, which has been going on for several decades, in fact.

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And this is not a U.S. phenomenon. 2004 marked a 20 year low in introduction of new medical therapies--in other words, novel medical therapies into worldwide markets. Costs--at the same time that this slow down—we're observing a slow down around the world--and FDA, of course, has talked to the regulators, whom we know well, all over the world, Australia, et cetera, et cetera, and Japan, the Europeans, they're all saying this and are very concerned about it.

The costs to get a drug—a new molecular entity drug onto the market has exploded. Some people—these numbers are controversial but it really doesn't matter--the order of magnitude is correct, estimate that for every successful new molecular entity that has gotten on the market you have to invest about $1.1 billion and a lot of that is investing in the losers. It's about nine losers to every one successful product.

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Now for the purposes of society, even the broader society, worldwide society, the point is here this is disincentivizing investment in less common diseases, in smaller markets or in risky innovative approaches. Actually, I believe, except for the Gates Foundation and other charitable efforts we've seen recently, the interesting investment in, for example, treating tropical diseases has declined, oddly enough, over say a decade or so but when you look at the risk here, the financial risk that's borne by those who attempt to introduce these new products, you perhaps understand the structure.

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And in the face of all this new science, which is incredible new science, the product development success rate has actually declined so the risk is higher now.

New compounds—this is for drugs and biologics—entering Phase I development today have about an eight percent chance of reaching the market, less than one in ten. It had about a 14 percent chance 15 years ago. Now you might say those numbers aren't that different, and I agree they aren't that different but shouldn't we be doing better now than we used to be. No, we're doing—arguably we're doing worse.

Even more concerning is the Phase III failure rate. This is figures that industry tells the FDA. It's now about 50 percent versus about 20 percent a decade ago. In other words, half the products—the drug or biological products that are taken into the latest stages of development where there is the greatest sum cost, half of those will fail. They'll either be ineffective. They have an unexpected toxicity or their benefit will be so marginal they'll be deemed commercially nonviable.

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Now, again this—and contributes to the costs then of developing these new therapies.

When FDA looked into this—we feel that the problem here—we had long been blamed for a lot of this. Okay. So we had some maybe vested interest in looking into this. Biomedical discoveries are not being effectively translated from the bench to the bedside, and I think the numbers speak for themselves.

There's huge investment in biomedical research. There's a lack of corresponding new products available to patients. There are major increases I medical product development costs and a concomitant major rise in health care costs because, at least for the pharmaceutical and device sector, they have to obviously pass on their development costs into the products, their R&D costs.

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There has been a lot of speculation on what's going on. A lot of people think, and this is undoubtedly true, that genomics and other new scientific advances are not at their full potential. Unfortunately, our experience is it takes 10 to 15 years for some new scientific advances to really be applied, if they're just left to their own devices more or less, to benefit a development fully.

Some people say easy targets are taken, such as bacteria. There were naïve bacteria out there that were just waiting for penicillin. Chronic diseases are much harder to study and much harder to intervene on. That's obviously true.

There's also the issue that rapidly escalating costs and complexity decrease a willingness of sponsors and their ability to bring a lot of candidates forward so we're probably screening fewer than we were or not that many more candidates in people.

Mergers and other business arrangements have decreased the number of duplicative candidates that are developed because companies typically pick one when they have a portfolio of similar candidates to move forward.

Of course, some people still blame the FDA for this. It is absolutely true if there were no FDA requirements and you could put anything on the market you wanted that some people would do that without any testing whatsoever and the translation would be extremely efficient. However, there might be other societal tolls that would be taken by that approach.

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Our diagnosis at the FDA is that we've kind of outstripped ourselves that the investment and progress in basic biomedical science has really far surpassed investment and progress in medical product development, which is in itself a separate different process. The development process

which we feels is the critical path between these discoveries and benefiting people in this country is becoming a serious bottleneck to delivery of new products.

Our explanation for this, to some extent, is that we are using the evaluation tools and the infrastructure of the last century and in some cases more remote than the last century to develop and evaluate this century's advances. So if we have new genetically discovered compounds and they go through a tremendous amount of sophisticated screening to look at their actions on receptor and so forth then we'll put them into animal toxicology to try and predict their safety in humans, animal toxicology being a science that has been around an extremely long time that hasn't changed very much in a very long time.

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So we feel that the science used to predict and evaluate product performance has not advanced at the same rate as basic science. In other words, that basic science hasn't been pulled in efficiently and applied to evaluating these products so this is causing developing to be the bottleneck.

We think, though, this is also an opportunity. There's an opportunity to improve product development with a new science but this is going to require a lot of paradigm shifts in the way we develop this applied science, something that we really haven't paid a lot of attention to in the past. "We" meaning the whole research enterprise, not the FDA.

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So we define a critical path as that series of steps that goes from candidate identification where you have a prototype device or you have a candidate drug or set of candidates all the way to where you get something on the market and there are a huge number of steps and it's extremely complicated procedures and efforts that have to be gone through to go from having that great idea. I cannot tell you how many times on this very campus I've talked to a laboratory and they've said, "I've discovered this and next year it's going to be available to patients." Of course most of these never become available to patients and there is a tremendous lack of understanding in the research community about what actually needs to be done to create a viable commercial product that actually can be marketed.

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It involves serial evaluation of the performance of the product through preclinical testing and clinical evaluation. If you look at it that way, whether it's a diagnostic device or whether it's a new type of imaging machine or a defibrillator or whether it's a drug or biologic or vaccine, you want to first predict how it's going to perform in people to make sure it's going to be safe enough to test in humans, and then you want to evaluate it in people and evaluate its performance to extrapolate, to be confident that you can extrapolate that to the wide number of people who will be exposed after marketing. That's really the task. It's a scientific task of evaluation and prediction and we don't have very sophisticated tools to do this. That's what I'm telling you.

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The Critical Path Initiative that we have developed focuses on the science that's used for these evaluations. It says how do we do these evaluations now? How can we do them better in the future?

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And, interestingly enough, a lot of the answers we've come up with have to do with genetics, genomics and personalized medicine, and I'm going to talk about that a little bit more, which I do have time, which is good.

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Here is a schematic of the Critical Path as we see it. Basic research is far on the left there and out of the research laboratories come prototypes, device prototypes or whatever, come discoveries of targets and candidates that could potentially intervene on those targets to make drugs or vaccines or biologics. After those are refined a bit, you get into preclinical development. Starting right about then you're on the critical path. You've identified something and you want to start trying to figure out whether it is going to perform adequately enough to be a new intervention. You have to take that all the way through what people are familiar with, the Phase I, II and III of clinical development and so forth, or some iteration of that, along with you have to file a marketing application, and then you have to get the product approved usually if it's an FDA regulated product obviously.

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Now, what people really don't understand is that the science used to do this is different than either basic research science that's on the left or we've heard a lot in the past four years about translational research. And I was somewhat befuddled by this and I did a literature search on translational research and I've looked at what the NIH is doing and everything, and that's usually defined as research that moves a single product or set of products from the bench into early clinical development. So again translational research is often focused on what is needed to be done for a specific product or class of products to move them into the clinic and evaluate them in the clinic. That's very different than the tools that you would use to do that and that is what we're saying is a somewhat neglected aspect of science.

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We found that there are really three dimensions that you have to get your product to perform on and FDA is extremely familiar with all of these because this is our bread and butter. This is what we do all day.

First of all, you need to assess safety. You need to assess safety preclinically before you get into people and you have to have a pretty good prediction of that or you're going to get into trouble and you're going to expose human volunteers to excessive risk.

And then, of course, during clinical development you have to get a fair amount of certainty about safety performance of the product before it's set loose on the population.

The second one, proof of efficacy, is what people have spent historically most of their time thinking about and worrying about, and that's how do you show that the product works. Basically that it benefits people in the way it is intended to. And that's why you do randomized controlled trials and so forth.

And then the third issue has been completely neglected, in general, except in the industrial sector, we feel, and that is what we call industrialization. How can you manufacture a product at

commercial scale with consistently high quality? And you may not believe this but this is not at all easy and if you think back to the flu vaccine problem a couple of years ago you can see that even highly motivated manufacturers can have problems with mass production of complex products.

FDA sees this over and over again. We have a constant stream of recalls and product quality problems that we are presiding over all the time. And shortages all generated by this industrialization problem.

This, for example, in genetics can lead to problems say with performance of diagnostic tests. If they are out of spec, they won't give you the right answers anymore potentially and we see this occasionally where we're recalling diagnostic tests, for example, because they have been manufactured improperly.

So these there challenges or dimensions on the Critical Path have to be serially addressed at greater and greater levels of performance all the way up to where the product is on the market where a very high level of performance needs to be sustained.

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Our initiative is a serious attempt to bring attention and focus for the need for all of us as a society to target some scientific efforts on modernizing the processes and methods that are used to evaluate these dimensions as the products move from selection all the way to mass manufacture.

I'm going to tell you a little bit about what FDA is doing in that and then I'm going to focus on personalized medicine.

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What we are doing is trying to stimulate, and we've been actually pretty successful in this, collaborative efforts among government, academia, industry and patient groups to get a lot of this work done. The work is focused not on product development, and that's what's very novel about this, this is focused on the infrastructure and the new scientific tool kit that we can all use to bring these products forward.

We're trying to build support for the academic science bases in the relevant disciplines. Some disciplines have really withered over the past 20 years with a focus on sort of reductionistic basic science and that has been fine. We have learned a tremendous amount from it. However, now we need animal physiologists. We need system biology. We need system understanding again and we lack some of those disciplines, clinical pharmacology and so forth. This one has been hard for us to do because these disciplines need financial support obviously.

One of the great tragedies that has been occurring, we think, is the lack of sharing of all the existing knowledge and databases that have been generated mostly in the private sector and not been shared. So we have a lot of information and data out there. We have very little knowledge that we've built on. If we have time, I can tell you about an animal genetic testing consortium that is going on for animal predictive safety tests and it's very interesting.

Finally, we need—then FDA needs to take this new science and turn it into new standards that then would be harmonized internationally and accepted in regulation around the world.

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What we've done is we published an initial report in '04. We had a long public discussion with both advisory committees, with the scientific community, with the industry and so forth. We started at that time initiating multiple public-private partnership consortia using nonprofit conveners to bring together these various sectors. As I said, we have been successful in this.

Recently we published the Critical Path Opportunities Report and List that can be found on FDA's website under Critical Path. I can get you a hard copy if you'd like. This is an analysis of the situation in fairly extensive detail plus a list which has 76 distinct opportunities, scientific projects, that we think should be completed that would really help move products to patients in a much more effective manner. Quite a few of those have to do with genetics in one form or another. So we're working to continue to form these consortia to do the—actually get the research done that's needed.

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Now we identified a number of opportunities for modernization of the process and here they are listed here. I'm only going to talk about biomarkers after this but these things are linked. Particularly the way we do clinical trials is going to have to change as we develop new biomarkers and bioinformatics is going to be needed extensively to support all this work in the future. I can tell you that neither of these structures—infrastructure elements are in place. We are working with the NIH, of course, on much of this and they've been very helpful.

But in biomarkers in vitro diagnostics is an extremely important aspect of this initiative and something we focus quite a bit about on to. Imaging is also a new and very important modality in the sense that we're going to move away from simply anatomic imaging, which is the kind of imaging that has been done mainly in the past, and we're going to be into functional imaging. We can look at different molecular probes of different types to look at physiology, pathophysiology and so forth using new kind of imaging technologies.

And then preclinical toxicogenomics, just to give an example of how using genomics—the C-PATH Institute, which is in Tucson, Arizona, that's headed up by Ray Woosley, and was founded to support critical path activities--it's a nonprofit—has formed a consortium as one of their projects. I think the—I believe they have 10 or 12 major pharmaceutical companies in the consortium right now. What they are doing is they have developed a mechanism with all the appropriate intellectual property and antitrust arrangements for these companies to pull their assays and data on animal toxicogenomic tests and related tests that have been developed to better predict toxicity in the animal testing.

What they will do—they're going to round robin cross validation testing using each other's assays in their own systems to look at their predictive value and then they're going to select the highest performing test, and those will be submitted to the FDA to hopefully begin the start of a new battery of tests to look at major organ toxicity in animals to better predict human safety.

Some of these tests, depending on how accessible they are from kind of the periphery of the organism, may then be used for human testing as well to monitor and predict human organ toxicity. So that is a very nice consortium and the point is—the real point of it is all these tests and data which are very cutting edge and using the most modern science were sequestered away in different pharmaceutical companies had not been shared, the data were not available, this

consortium will make all its data and the assays publicly available at the end of their testing period.

So we're trying to set up consortia in all of these areas and we're slowly—the FDA does not have any funding to do this initiative, although there is some money in the President's 07 budget and we are hopeful perhaps we will receive some funding to do this initiative in '07.

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Now I want to talk about biomarker qualification because this is the heart really in my mind of personalized medicine. Biomarkers can be defined as quantitative measures, a physiology, pathophysiology, all sorts of stuff. Quantitative measures of something about the person and their biology. An example that we have now are things like liver function tests, ECGs, x-rays, psychological tests. These are quantitative biomarkers that we use to assay some state of the individual.

The problem we've observed in the past 20 years is that biomarker discovery is fast. If you read the medical literature and scientific literature, you'd believe there are thousands of desirable and wonderfully predictive biomarkers out there, and we can tell everything about people based on all these biomarkers that have been discovered and their wonderful associations. Unfortunately, clinical meaning develops very slowly as an understatement. Not at all—okay—might be a better description of what happens with biomarkers. We get all this very tasty, suggestive publications that are written up in the newspapers and the public thinks, "Oh. We're going to be able to tell whether I'm going to have an MI in the next week or so or whether I'm going to get ovarian cancer," or all this kind of stuff, and yet 10 years later nothing. We haven't advanced any further.

And then, of course, you can always blame the FDA for this. The FDA hasn't approved them but we're finally pushing back and saying, "We don't approve things that don't have data associated with them."

The problem—the reason that clinical meaning develops very slowly is to really understand the clinical performance of a biomarker means you have to study it and it is expensive and it is grueling and it is not considered novel say by funders. It's not something that you win Nobel Prizes for doing.

But new biomarkers are key to personalized medicine because, I think, as Americans, we tend to forget—although I'm sure this committee doesn't forget—but that diagnosis is the foundation of medicine, not treatment. Okay. And you really have to know what you've got before you intervene and we have been rushing to develop treatments and we have not been rushing to figure out all the things we need to know about people before we intervene and treat them.

But there are very few parties that have the wherewithal to develop new biomarkers clinically and, therefore, that's why we think consortia are needed to develop them because there are many parties that will benefit from their development, not to mention the patients.

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So by "successful biomarker qualification" we mean understanding the biomarker's utility or fitness for any given use. One of the problems with biomarkers that everyone is obsessed with is surrogate endpoints, which are biomarkers that could be used for drug approval in lieu of effectiveness. That's almost irrelevant to what we're talking about here. What we're talking

about here is understanding pathogenesis, for example. We're talking about understanding biology using these diagnostic probes.

New biomarkers obviously are critical to clinical medicine, I believe, to its efficiency and effectiveness, and efficient product development. So this is a place where I believe that kind of the stars are lined up that the manufacturers of therapeutics have the same stake in the development of new biomarkers that the insurers, patients and the public do, which is we all need them and they will tremendously improve medicine if they can be developed.

But as I said there is no single entity charged with accomplishing qualification. As you all are probably acutely aware, the diagnostic companies regard their task primarily as analytic validation while making sure that the test performs and analyzes the analite correctly. That's a very important step but it doesn't tell you what the analite means but we all have a big stake in making sure this gets accomplished and this is a big part of critical path.

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What am I talking about? I can get extremely concrete but I was only given a half hour or something like that so I will—how long do I have by the way? Until 10:30 or am I over my time already?

DR. : No, you're fine.

DR. WOODCOCK: Okay. Good. Okay.

What I mean is, for example, in pharmacogenomics—the very simple one is the pharmacogenetics, okay, that have to do with just the gene sequence and variability and the gene sequence could even itself, leaving aside genomics, be an extremely powerful tool for development and also for improving the quality of health care.

Many of us have differences in how we dispose of drugs after we take them. I imagine some people in this room are laypeople. Okay. So actually lots of doctors don't know this so this will be very comforting to you but if we all in this room took a drug, all right, some of us if we took an average dose would get the average blood level, the average exposure, okay. Others of us might get five times that level. Okay. Why? Because our disposal mechanism is different due to genetics. We dispose of the drug much differently, much slower. And those people are the people who get a lot of side effects obviously from some of these drugs. Other people who are rapid metabolizers—in other words, their disposal mechanisms are hyper efficient—they get no detectable blood level at all from taking an average dose. So they might as well not bother. Okay. They are just chewing up the insurance company's money. But it's really those people who have variable levels of metabolism. It's not average that are exposed to higher risk.

The Center for Devices at FDA has approved some of the—Steve Gutman and company have approved some of the first drug metabolism polymorphism tests. They are available. They can be applied to, for example, very important drugs such as cancer drugs where there's a lot at stake. You really don't want to have four to five times the blood level for a drug that has a neurotherapeutic index.

FDA right now is looking at trying to do a clinical study on blood thinners, warfarin. Warfarin is one of those compounds that is obviously associated with a lot of side effects. It requires a lot of testing and fussing over by the health care system to keep people from getting into trouble and yet

maybe about 40 to 50 percent of the variability in the response to warfarin is genetically based and now there are tests available. They are not quite commercially available and they're not FDA approved tests, in general, but there are tests that can sort this out. But people have told us, and rightly so, they would like some documented proof of this and so a number of parties are pursuing doing some clinical trials to look at how much we can improve warfarin outcomes using pharmacogenetic directed dosing.

So that's drug metabolism polymorphisms and there are many others so there's a big opportunity here. A lot of these are for approved drugs.

For example, a long time ago FDA—when we approved the tricyclic antidepressants, the recommended dose was 25 to 250 milligrams. You say, "How can that be? What kind of recommended dose is that?" Well, that was because those drugs were subject to polymorphic metabolism and so you had to titrate everybody around probably for a long time. These may be people who were severely depressed, though. This was a very bad situation in the sense that many of them needed urgent intervention.

So that field is coming along. FDA—between the Center for Drugs and Center for Devices, we have done like a huge amount of things, which you may know about and your subcommittee may have talked about, to try and push this along because of the implications for safety of the populous and better development of products.

The second large group of tests would be predictors of drug—genetic predictors of drug response or nonresponse. In other words, this is targeting therapy towards those who would respond or away from those who don't stand to respond to a given treatment.

Again, the industry, the pharmaceutical industry, was not very enthusiastic about this for a long time because this would narrow the population, maybe about 50 percent, maybe in some cases 90 percent of the people who would currently get the drug won't get it at all. Okay. But from a societal point of view that's good. Okay. We don't want to give drugs to people who don't respond and I have—I ran the Center for Drugs for 11 years and I can tell you that the treatment effect of many drugs is very small but that's probably not because they don't work. In most cases it's because there are a lot of people in there who may not respond to the drug. So if we could find a way to weed those people out and not expose them that's targeted therapy and that, again, is personalized medicine.

Cancer is probably on the cutting edge of this. The problem with cancer is you're looking at the tumor. It's hard to get pieces of the tumor all the time to keep testing it to see whether it's going to respond to various therapies or not but cancer—we are working in cancer in consortia to try and get some targeted tests for targeting therapy developed.

And then a third category is genetic basis of adverse events. We're working with NIH and with the pharmaceutical industry on this, especially some of these rare very serious adverse events. We've always said they were idiosyncratic and that's a doctor's term for meaning we're stupid. We're too stupid to know what causes them so we call it idiosyncratic. But, of course, everything from a scientific standpoint has a cause and some we believe are these very serious rare adverse events that cause drugs to be pulled off the market. Probably everybody doesn't get a side effect. The vast majority of people don't get the side effect, just some people. And so there's some reason and we think in a number of cases there's a genetic basis that we can sort out.

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Advanced imaging is another thing that we're going to see more and more frequently. We may get imaging that can distinguish, frankly, certain genetic abnormalities at some point in time but we're not quite there yet.

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Now how much more time do I have? Be honest with me. Should I just wind up right now?

DR. WINN-DEEN: It depends on how long you can say after you finish.

DR. WOODCOCK: Okay. I can stay. I can stay as long as you like. All right.

DR. WINN-DEEN: So we're scheduled to take a break at 10 something, 10:35, which is almost where we are now so what I'd like to do is let Janet finish and have a short Q&A and then we'll take a break maybe a little bit later. That just moves our discussion off a little bit for the late morning.

DR. WOODCOCK: I'm sorry. I don't mean to go over.

DR. WINN-DEEN: No problem. No, we're delighted to have you.

DR. WOODCOCK: There's so much one can say about this. I feel that people need to understand if you're talking—I'm shifting a little bit to personalized medicine giving this whole thing as background that I just showed you, the role of genetics in the Critical Path Initiative.

We have to recognize that the way we look at drugs and devices and biologics and everything in development—the development is the parent of the clinical use or the clinical use is a child of the development process, however you want to look at it. So the way we approach things now leads to much of the way they're used in health care.

What we do now is the randomized controlled clinical trials to determine efficacy and to a great extent safety. And these were really scientific—what we used to do, which embarrassingly enough, up to '60s, we basically used sort of anecdotal reports to—I don't mean "we" FDA. I mean "we" the society used anecdotal doctor's reports to determine how well things worked. So this is really what has lifted medicine up into its current state of science but don't forget this is a population-based model that's used to control for not only bias but the impact of variability. Much of the—a lot of this variability actually is something that we'd like to know about nowadays. This is at the heart of personalized medicine so instead of controlling for variability simply by randomizing and then making all the recommendations just for the population that you enrolled, you really would like to understand the variability. Part of the problem, though, is we've gotten so enamored of the randomized clinical trial and how we do that on this population basis that I believe we've stopped thinking about the fact that many of these variations are actually extremely informative.

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Now there are limitations to controlled trials and that's what we're up against as a society. You can answer theoretically any question with a controlled trial. You could decide whether to get up in the morning, probably by using a controlled trial, but it's not an efficient way to do business. You can only answer one or a few questions per trial. Unfortunately, there's an unlimited number of questions about the appropriate use of medical products and about the outcomes of use of

medical products and these questions change over time. They are not static but there is a decidedly limited universe of funding patients, investigators, time and resources to conduct randomized, controlled, empirical trials to answer all these questions. If you read the medical literature, they always use a ritual phrase at the end of every article, which is more research is needed on this question to answer it definitively.

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Now this is true then for medical product development, drug development and other development. Okay. We're making compromises when these things are put on the market because it is impossible to answer all the questions. In fact, at the end of most drug development programs and biologicals, after these huge expenditures of resources that I've told you and also huge expenditures of time, it might be seven years or so, we don't know very much about the product. Everybody has been criticized a great deal about this recently in the drug safety uproar and so forth but this is the facts because we've done a lot of randomized trials and we've done a lot of empirical study and we do not have a lot of mechanistic knowledge.

We're usually quite confident that the drug or biological has a measurable beneficial effect in a described population of people who are treated in the trials but the overall treatment effect is often very small and we don't know, for example, often whether a few people responded a lot or whether a lot of people responded a very tiny amount, and that's extremely important as to whether you actually want to use that drug on people in the future but that isn't really how it's set up now. You can have a very tiny response and a lot of people and get a statistically significant result.

But as a result of all this, which I still want to emphasize is the best we've ever had and is a scientific triumph, nevertheless, often many people who take drugs after marketing don't benefit—aren't going to benefit from them.

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So we—I'm going to skip over this. I don't have enough time.

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So this leads—this whole empirical approach to medical product development leads to a lot of things. It leads to part of the health care cost controversy because we can't quantify the actual value of products in the marketplace. I think that we're—and this is something, I think, this committee needs to evaluate that the health care policy community, in general, has a very pessimistic attitude about technology and believes it leads to greater expense, lower productivity in health care and maybe not better outcomes for patients.

So the implications for genetic testing, for example, I think, are very important and whether people are actually willing to pay for that.

This also exacerbates a lot of the safety controversies that are out there because products are viewed as safe or unsafe for the entire population. There's no appreciation of the effect of human variability and its affect on safety. The reason is because we don't know those relationships.

Finally, I think, in health care quality this—I'm a physician and I learned a tremendous amount as I did drug regulation and I really think that all the confusing results and conflicting reports we

have out there based on all the empirical tests that we do and so forth lead to an anecdotal approach to care. You can think of the estrogens, for example. I think physicians just think I get so many conflicting reports that I just can't sort my way through this and I'm just going to do whatever my anecdotal experience tells me is the best thing to do.

(Slide.)

What we need to do in development to help this situation is have more—pair more diagnostics with therapeutics as they're coming through the pipeline and a lot of this means more genetic and beyond genetic, probably proteomic and so forth evaluation. We need to identify—both identify the response of subgroups and prevent toxicity.

In other words, to put this a different way, we need a more mechanistic model of how products work. We need to put all our effort really into developing as much mechanistic understanding as possible. To do this we're going to have to change the way we do trials to have adaptive designs so we can answer lots of questions in the trials rather than just answer one question. Those questions are going to relate to who should be treated, who shouldn't be treated and so forth in a serial manner.

(Slide.)

For the development process then, this can improve the success rate, which is like the most terrible problem the development process has for drugs right now, and lower development costs but at the same time having products come out of the pipeline with more information rather than minimal information but we need to continuously improve development science and processes or this slope I showed you at the beginning of this talk is going to continue downward.

(Slide.)

But for patients this will result in more personalized treatment. What we need to see is much larger treatment effects using targeted therapy. In other words, if you have cancer or whatever and you are going to have your tumor treated with a certain regimen, you need a very—we need to move to where there's very high probability of a positive response.

We also, with many of these biomarkers, will be able to stop therapy that is ineffective faster. Right now, again, treatment is empirical. We just take the population. We expose them for quite a long time and maybe they respond and maybe they don't, and then we switch them. Using biomarkers we'll be able to interrupt that cycle much faster.

Avoidance of side effects and injury from these products through prevention and better and earlier product availability, and overall I think this will lead to higher quality health care as we have more mechanistic understanding of our treatments rather than empirically treating people.

So I think we hear a lot about improving health care and health outcomes in this country through all the things people talk about all the time over on the right hand here but I think the left hand, the development process, which is completely ignored almost in most health care policy discussions, is another pathway to improve health outcomes by doing a more scientific job on the development side so that's what I have to say.

Thank you very much.

(Applause.)

Q&A

DR. WINN-DEEN: Thank you, Janet. Could you take maybe five minutes of questions before we take a break?

DR. WOODCOCK: Yes.

DR. WINN-DEEN: I just want to see if anyone on the committee—Debra, then Julio.

DR. LEONARD: Very interesting. What is going to happen to the opportunities list? I mean, correct me if I'm wrong but I don't think of the FDA has a funding agency.

DR. WOODCOCK: Right.

DR. LEONARD: So is this linked at all to NIH funding? Is it linked to other sources of funding for these types of opportunities because it's a very exciting and interesting list?

DR. WOODCOCK: Right.

DR. LEONARD: But no one is going to do it just because FDA says, "Oh, wouldn't that be cool?"

DR. WOODCOCK: Right. Well, what we think was that—see this was a problem that nobody knew about in some way and what we needed to do is reduce—we discussed this problem in our first Critical Path report. We wanted to reduce it to some level of concreteness so people would understand what needed to be done. And, no, FDA is not intending to do almost any of this work. Sometimes we do laboratory research for product characterization issues in the manufacturing so we develop the standards for product performance in the manufacturing realm but the clinical work, the toxicology work, we're not going to be able to do that but people are stepping forward. I mean it's slow but we're seeing a ground swell of people working on this in consortial arrangements. We are working very well with NIH and we think that as people begin to understand this problem and the criticality of this to health that this will build over time but we don't expect this to happen overnight.

DR. COLLINS: So I very much agree that this is an area of intense need and I think what FDA has done here by outlining the agenda is an extremely helpful step forward. It is sort of an odd circumstance where having outlined the agenda, the FDA is not in a position themselves financially to push the ball forward and, therefore, are dependent upon building these consortia and working with other agencies. Obviously that in some instances slows down the process because you have to cajole instead of offering the bucks that might otherwise stimulate the process and perhaps that a bit of an unusual circumstance.

I think the need is so great that you do see various organizations rallying to make this happen and certainly NIH has been enthusiastic about many of these priorities and has been working closely with FDA to try to make them come forward. The mention of the warfarin trial, for instance, is something that we're trying to do together which I think will be actually a very interesting poster child for prospective pharmacogenomics.

I guess, Janet, could you say a little bit more about the Critical Path Institute as another player here in terms of an organization not for profit that by its very name is designed to try to fill some of this void and how are they funded and what kind of opportunities do they have and where do you see the challenges for that organization in terms of just stepping into the void here and making all this happen?

DR. WINN-DEEN: Well, the C-Path Institute is a 501C3 nonprofit. It's funded for its staff and so forth by the City of Tucson, the State of Arizona. It's funded by nonpharmaceutical, nonindustry sources, and charitable funding as well. For projects it's putting together a consortia that would be funded by the various partners for the projects themselves and the toxicogenomics is obviously the one that is farthest along but they are doing—they got a small earmark in FDA's budget this year from congress to do genetic cardiac safety biomarker work using the University of Utah's large genetic database that they have. So that work is ongoing. As well, they're participating in the warfarin project and they're also starting to work on targeted therapy and putting together a consortium on that, which is very exciting. But we do not see any one source being the central group doing this. We see a wide range of groups around the country working on different projects depending on the level of interest.

DR. WINN-DEEN: I think Julio had a question.

DR. LICINIO: Yes. I had a question about the issue of safety that you presented in one of the last slides because it's such a—nothing is completely safe.

DR. WINN-DEEN: Right.

DR. LICINIO: And where do you draw the line? Especially with pharmacogenetics it can become complicated because what's safe for one group may not be for the other and then you get into the accuracy of the test and are the people going to take the drug irrespective of the testing results.

DR. WINN-DEEN: Right.

DR. LICINIO: So can you make some comments about this issue and how—I think now especially—I don't know if you have the same impression that people have this expectation of increasing safety but nothing is completely safe and it's never going to be. So how do you—where do you draw the line? Where do you draw the expectation then and the line from the regulatory perspective?

DR. WINN-DEEN: Right. Well, of course, no medical product is ever going to be completely safe and has a benefit/risk analysis associated with it. I think we can improve the benefit/risk remarkably. If you have an expectation of significant benefit, even if the risk remains constant, your judgment of the overall benefit/risk for you is improved.

I think, though, that pharmacogenetics and genomics and related sciences will improve the safety and I recognize I've heard these concerns many times. We don't know the link between that and clinical outcomes. People won't have the tests. Other people will take the drug regardless. That's all true. But I'll tell you it's better than guessing and that's what we do now. We have no idea why people get adverse events and what are the risk factors in a given population. Except for you could say age, debility, multiple medications or so forth. We don't have the mechanistic links between bad outcome and some kind of genetic or other predisposition.

The more mechanistic understanding we have both on the efficacy side as well as the safety side the better off we're all going to be. I really strongly believe that.

DR. WINN-DEEN: Reed, did you have a question?

DR. TUCKSON: First of all, again, thank you very much. I mean your first slides are actually mind blowing. I mean, I don't think that—at least I don't think many people—I certainly know that I did not understand that with all of the research that's going on, all of the stuff that's coming down the pipeline into clinical medicine today that is expensive and complex that the actual fall off in the amount of stuff coming to you all is that dramatic. I mean, it's astounding information for those outside of your world.

Now having said that then I think your—if I understand the big 8,000 foot level of your point that—maybe it's two, and one is that part of the problem is that there needs to be a more precise ability for developmentors, manufacturers to predict earlier on whether or not their product has actually got a dooby-squatch chance in heck of working so they can target their efforts more effectively, which is a big important industry deal.

And then, secondly, they have to be better tools for you to evaluate them to be able to do that more quickly, more efficiently and more effectively.

So if those are the two big take homes here then I think the committee needs to sort of be thinking about what we—if there's a role for us here and what that might be to be able to go forward. First of all, this has been enormously good just as we understand and learn this and begin to think about what pharmacogenomics means going forward so I think that our challenge is, as you are in the break and as we start to have discussion coming back from the break, is what can we do with this.

I think Francis' question about is this the time for—he has given us some sense that there's some cross HHS coordination now. I suspect that, like most things, we might be able to urge a finer point on that, I mean, but it sounds like that's encouraging. Either we need to support that to the Secretary or urge some new things to be done or some more energy be on that.

I think secondly coming out of what you sort of said, Janet, is the sense of some industry—some multi-stakeholder conversation about this, which sounds like it's in everybody's interest, not only the folks who are in the industry but those outside of the industry and perhaps that is something that we might want to kick around after the break.

DR. WINN-DEEN: I would add there's a third high level point, I think, which is, number one, there's a huge problem—the pipeline problem. Number two, we need these better tools at the manufacturers and we need the evaluative tools.

Number three, I think it's really important that this has the potential to transform the way clinical practice is done if we can gain more understanding of what we're doing with therapeutics.

DR. TUCKSON: By the way, Janet, I sort of wanted to give you the chance. I don't know whether you can in public any more but the sort of sense of the degree to which you feel that the collaboration with—I sort of made that rhetorical as opposed to whatever a question is—but is there anything else that you might want to say in terms of opportunities that you see either now or later for more coordinated activity across the enterprise, including the Agency for Health Care Research and Quality?

DR. WOODCOCK: Yes. We're having terrific collaborations. I think an unprecedented level of collaborations I would say with NIH and the various institutes around these issues because at the same time that—I mean we have the Roadmap Initiative pushing on one side on the translational centers and on other things but here we have the basic sciences really starting to intersect with the therapeutic science, the clinical science, in a way that we haven't seen before. We can actually start making those links in a much more direct manner and, therefore, I think there's a real opportunity to collaborate.

I think a lot of this is limited right now by FDA's extremely limited resources.

DR. WINN-DEEN: We'll take one more question before the break. Steven?

DR. TEUTSCH: That's great, Janet, and appreciate all your thoughts about this. I'd like to ask you if you couldn't comment a little bit, though, about what we continually call the fourth hurdle in drug development, which is getting it out and demonstrating its value particularly to payers.

DR. WOODCOCK: Right.

DR. TEUTSCH: And payers, of course, are becoming ever more sophisticated, which is great from the societal perspective and they want to see outcomes and they want to see incremental outcomes.

DR. WOODCOCK: Right.

DR. TEUTSCH: And some of the things that you're talking about obviously can do that for subpopulations and becoming more specific but as we know currently only about 30 percent of the things that actually do get into the marketplace are commercially successful today.

DR. WOODCOCK: Right.

DR. TEUTSCH: And this is going to become that much more challenging if we, of course, get them for ever smaller populations. So the genetics and the kinds of things you're talking about will be—will hopefully get some efficiencies on one level but it's still going to be a real challenge to get those kind of outcomes, particularly with the challenges in biomarkers like you said. The biomarkers, of course, are only one intermediate. I mean as you were mentioning coumadin, you can look at the genetics but we all know there are so many factors that lead to differences in coumadin level. You sort of ask yourself why don't you just measure the coumadin levels rather than having to—looking at just again one piece.

I think the challenges of all this are great and clearly the kinds of things you're talking about are a major step in one part of it but it raises—the industry is under a lot of challenges of this sort to figure out how to make this all work in a commercially successful manner.

DR. WOODCOCK: Right. I agree. I have listened to several health economists present analyses of the economics of this new way of doing things and with some very modest assumptions on the pre-market side that is an increase probability of success. I already presented to you all at least for drugs and biologics how low the success rate is now. You can improve your probability of success modestly if you are targeting. The economics are favorable. I think this is why a number of large companies have started pursuing targeted therapy.

Also, the economics would be favorable if you can improve the treatment effect significantly because then you have demonstration of the value of the treatment a priori.

But the devil is going to be in the details on all of these and having talked to the insurers I think we're going to have to demonstrate a lot of this in clinical outcome studies that show the benefits, not just—I'm obviously—because having run the Drug Center, we approve all generics based on blood levels. So I believe that if you can—the blood levels are an adequate and well validated surrogate for effectiveness and safety but everybody else apparently doesn't believe that even though they push generics all the time. I mean if you can show that through pharmacogenetics you can tighten the blood levels very significantly. That's good enough for me but it obviously is not good enough for the outside world.

So we're going to have to do some outcome studies and some other things. Like everything else, this is going to take longer and be a rockier road than we all might hope but the promise for patients is so significant that we have—I think we have no other choice but to like push this as hard as we can.

DR. WINN-DEEN: I think that's a perfect place to stop.

We're going to take a ten minute break and come back about five after 11:00 and we're going to start with the recommendations that pertain to FDA while we have Dr. Woodcock here to help with that discussion.

(Whereupon, at 10:58 a.m., a break was taken.)