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FOOD AND DRUG ADMINISTRATION'S CRITICAL PATH INITIATIVE

HEARING

BEFORE A

SUBCOMMITTEE OF THE

COMMITTEE ON APPROPRIATIONS

UNITED STATES SENATE

ONE HUNDRED TENTH CONGRESS

FIRST SESSION

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FOOD AND DRUG ADMINISTRATION'S CRITICAL PATH INITIATIVE

FRIDAY, JUNE 1, 2007

U.S. SENATE, SUBCOMMITTEE ON AGRICULTURE, RURAL DEVELOPMENT, FOOD AND DRUG ADMINISTRATION, AND RELATED AGENCIES, COMMITTEE ON APPROPRIATIONS,
Salt Lake City, Utah.

The subcommittee met at 9 a.m., at the University of Utah, Eccles Institute of Human Genetics, Hon. Robert F. Bennett, presiding.

Present: Senator Bennett.

STATEMENT OF SENATOR ROBERT F. BENNETT

Senator BENNETT. The hearing will come to order. Good morning. We appreciate everyone being here. I want to give special thanks to the University of Utah for allowing us to use this auditorium, and to the Eccles Institute of Human Genetics.

This is an impressive facility, as we all realized when we walked in it. And the staff here have been wonderful to work with. We especially thank Kim Wirthlin and Kaye Clark as well as Elaine Fry with the Eccles Institute. Senator Herb Kohl is the chairman of the subcommittee, and we meet here today with his approval. I'm grateful to him for scheduling this hearing.

I've focused on health care for quite a long time. Last month I cosponsored the Healthy Americans Act in the Senate with Senator Wyden of Oregon. It's our attempt to find a way to give all Americans access to health care with some kind of insurance coverage.

Senator Wyden and I both agree that health care discussions should focus on health. Most of the discussions are about payment systems and insurance companies and coverage. Prevention is worth a pound of cure, as the old cliché says. Like most clichés, it happens to be true.

When Americans need to go to the doctor, they should be able to get a treatment that is safe, effective and right for them. Often a treatment sometimes is right for one individual but not for another. And so we have asked the Commissioner of the Food and Drug Administration, along with some distinguished panelists, to be here today to talk about the role that FDA can play in keeping our treatments safe.

Now, in 2004 FDA called for a national effort to identify specific activities aimed at modernizing the delivery of health care, and they formally launched the agency's Critical Path Initiative. The term "Critical Path" is used to describe the way that a potential

drug or biological product or device can find its way from prototype or an idea to a viable medical product for use in patients.

The initiative was born out of the agency's concern for the declining number of new medical products coming to the market. One of the strengths of the American economy has been the constant flow of new products in this area. And when the number starts to drop off, that is a legitimate reason for concern.

The FDA has realized that many of the tools used to develop and review medical products today are outdated. They need to be modernized so that new forms of scientific data, like genetic information, can be applied to product development and ultimately to the use of these products in patients.

There's no place where you can come and focus on genetic information that's better than the University of Utah and the State of Utah, which is one of the reasons why we are holding this hearing here. I want to discuss the future of Critical Path, and I hope we'll be able to determine which proactive efforts FDA, the research community, and industry can engage in to bring the Critical Path Initiative along in the way it should go forward.

We're delighted to have the commissioner of the Food and Drug Administration here at the University of Utah. As I say, it's the ideal location for a discussion on these issues because the university is currently engaged in Critical Path research.

Now, particularly on the anticoagulant warfarin, this research program has been extremely successful. It's described as a good model for similar Critical Path research opportunities. The University of Utah is a leader in the study of human genetics. And we're going to have a panel of university experts mixing with the commissioner.

Given the right tools the Federal Government, academia, and industry can work together to speed the delivery of new products to patients in need, as well as pay attention, as it always has, to the safety and efficacy of these products, and products that are already on the market. Then incorporate new scientific approaches to lead to a more personalized and targeted therapy.

We're hoping that as a result, millions of Americans now suffering from diseases that don't respond to their present treatment can be helped. To give you an example: targeted research dollars can help get the right drug to the right patient to take some of the guesswork out of medical care, which would minimize side effects.

If you take a blanket drug, the side effects show up in some patients and then the whole drug is challenged. But if you can do the targeting process that we're going to talk about today, you can maximize drug benefits, increase efficiency, and at the same time lower costs.

Research done at the University of Utah on the anticoagulant drug warfarin has been estimated to reduce hospitalizations from adverse reactions and reduce health care spending by approximately $1.1 billion annually. And this savings is achieved through further understanding of the way in which certain people metabolize warfarin and integrate genetic testing into warfarin therapy.

Given this new tool, doctors can make a decision that will get the right dose of warfarin to a patient based on that patient's specific

genetic makeup. This is an exciting new frontier that I'm proud to say is coming out of activity here at the University of Utah.

And it's only one example. The FDA has already started working on 40 long-term projects to support the Critical Path Initiative. And with appropriate resources in the right places the agency can, through collaborative agreements, facilitate the development and delivery of therapies for such diseases as cancer, diabetes, and cardiovascular disease.

Those are the opportunities we're going to explore with our panelists this morning. We'll discuss the Critical Path Initiative and look for ways that it can lead to better medical products, personalized medicine, and ultimately lower health care costs.

Now, we always divide our hearings into panels. Our first panel is one man, Dr. Andrew von Eschenbach. He's the Commissioner of the Food and Drug Administration.

Dr. von Eschenbach, we're delighted to have you here at Utah, and we hope you find your stay, both at the university and in the State, successful and enjoyable.

The second panel will join with Dr. von Eschenbach, and I'll introduce them now. Dr. Ray Woosley, who's the president and CEO of the Critical Path Institute. Dr. Jeffrey Anderson, associate chief of cardiology at LDS Hospital and a professor of internal medicine here at the University of Utah.

Dr. Glenn Prestwich, he's the presidential professor and director of the Center for Therapeutic Biomaterials at the University of Utah. And Dr. David Jones, who's the senior director for Early Translational Research at the Huntsman Cancer Institute.

Dr. von Eschenbach, we will start out with you. And then instead of having you step down, we will have the panel join you and see if we can't make this a roundtable kind of discussion instead of the usual congressional hearing, with each panel just speaking back.

In this case you're speaking to the record because this Senator probably is not going to understand most of what you have to say. I shouldn't admit that in public, but I'm committed to full disclosure. I will do my best to catch what you're doing.

There is, of course, since this is an official subcommittee meeting, a full transcript being made. And if the witnesses wish to submit information for the record so that it can facilitate the testimony and the panel discussion, that of course will be acceptable.

Dr. von Eschenbach, we look forward to your testimony and hope you will be able to stay for the discussion round with the second panel.

STATEMENT OF DR. ANDREW C. VON ESCHENBACH, COMMISSIONER, FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES

Dr. VON ESCHENBACH. Thank you very much, Senator Bennett. And I certainly look forward to a morning of very full and very important discussion both with you and with the other members of the panel and also with the audience.

I have submitted for the record written testimony that addresses the very important role that the Critical Path Initiative will play in the Food and Drug Administration's commitment to protect and promote the public health and the welfare of the American people we serve. And I'd like to take my remarks this morning to really

summarize and emphasize the importance of this initiative, as it is a part of our appropriations request to your committee.

And I want to begin by thanking you, Senator Bennett, for your leadership and your willingness to convene this meeting, this hearing, to address this specific subject. You and Chairman Kohl have been strong and ardent supporters in support of the Food and Drug Administration. Senator Kohl's staff is here as well today. And it is extremely important that I express to you and other members of the committee the gratitude of the FDA for that support.

This particular initiative is, I think, very fitting to be discussed at a meeting, at a hearing being held here today in Utah. And it's not just because of the incredibly beautiful scenery, weather, and tremendous hospitality, but most importantly because of the setting. One might wonder why, if this is an important meeting, is it being held here and not in Washington, DC.

There's no better place for a meeting to talk about an initiative to secure the future of health, health care, and our health care delivery system than to do it here in a community, surrounded by the people we are committed to serve. And in an environment of academic excellence that has actually served to provide the scientific basis upon which this new future in health and in health care is based.

And so what I am here this morning to do is to share with you a bit of that vision for that new future. The role that the Food and Drug Administration can play in being a bridge to that new future by utilizing the tools of modern science and technology to help facilitate our ability to bring the fruits of discovery and development to those who are desperately in need of cures for disease, enhancement of their health, and the hope of a better and more healthful, healthy life.

I too want to thank the University of Utah for the hospitality in hosting this meeting. And particularly I refer back to my past life as the Director of the National Cancer Institute, where I had a firsthand opportunity to appreciate the excellence of this university, particularly its cancer center, the Huntsman Cancer Center, and the tremendous contributions that it is making to our national effort to alleviate the burden of a disease like cancer.

The reason why this hearing is so important and why the initiative is deserving of the support and the investment of the American people is because of the fact that we are currently in the midst of perhaps the most profound transformation to ever occur in the history of medicine.

Those of us who are physicians have inherited a profession where, for thousands of years, our only hope of being able to address the needs of a patient by taking care of a disease was based primarily on what we could observe using our five senses. We basically observed the manifestation of disease in terms of what we could see, what we could hear with the stethoscope, what we could perhaps feel with our hands.

And perhaps a hundred years ago we made a major step forward in that model of observation by now having microscopes and x-ray machines, but the fundamental principle remained the same. We were dealing with diseases based on the observation of the manifestation of that disease.

The recognition of disease told us very little about what to do about it. The observation of a lump in a woman's breast did not tell us what the appropriate therapy might be. But because of the investment this Nation made in science and technology throughout the latter half of the 20th century, we began to change that paradigm.

Because of the kind of work that's going on here at the University of Utah, specifically with the focus on beginning to understand genetics, and the genetic basis of disease and the genetic basis of life, we have moved from that model of macroscopic and microscopic observation to a model of molecular understanding of disease.

We now can recognize the genes and the molecules that are actually at the cause of the disease process. And with that new understanding, we have transformed our ability to now deal with diseases. Diseases like cancer, and Alzheimer's, and many others. We now have the opportunity, based on that understanding of fundamental mechanisms, to envision new solutions, new interventions, new drugs, new biologics, new devices, that can actually intervene in those mechanisms and be able to obtain a predictable beneficial outcome.

One specific example in my field of interest—oncology—was the fact that for many years, decades, we could recognize a form of leukemia called chronic myelogenous leukemia by observing or seeing a chromosome in the cell under the microscope. But we really could not do very much about that until the fruits of genetics and molecular biology allowed us to understand that what we were observing in that abnormal Philadelphia chromosome was actually a gene relocation and fusion that produced a cascade in a molecular pathway that was driving the unregulated proliferation of that cell, namely leukemia.

The knowledge of the mechanism driven by the—those abnormal genes, or oncogenes, allowed us to immediately recognize that if we had a drug that could intervene in that pathway, a kinase pathway inhibitor, we would be able to shut that cancer cell off. And in fact such a drug was developed and was approved by the Food and Drug Administration and became, if you will, the poster child for targeted mechanistic-based interventions in the disease process. This is but one example of what is now a widely growing and rapidly growing new portfolio of opportunities. But as Senator Bennett has pointed out already, the pathway to get the fruits and the benefits of those observations and that development to the patients, the people, the public, who desperately need them the most, is a pathway that is clogged by mechanisms and processes that are not equipped or prepared to deal with this new reality.

And so we must transform the pathway from discovery to development to delivery. And that transformation of that pathway is, in fact, the Critical Path Initiative. It is a series of tools using science and technology that will allow us to entirely revise and revamp our ability to develop and bring to patients the fruits and benefits of these new interventions.

This will have enormous implications and benefit, not only for improving the health and welfare of the people we serve, by similar examples of the one I mentioned with the revolutionary treatment

of chronic myelogenous leukemia, but also other diseases, like Alzheimer's and diabetes and a variety of others.

Even more importantly, it will lead to a transformation in our health care and our health care delivery system with not only the benefits of millions of lives saved and improved but also the reduction of costs. You will hear later about one specific example of that opportunity.

By understanding fundamental molecular mechanisms, not only in the disease but in the patient or the person with that disease, and not only understanding the disease process but the interventions and the treatments that we're using, we can now begin to create a system of health care that is predictive, preemptive, and much more personalized.

The drug warfarin that you'll hear about today is one that's widely administered. But just like many of the other drugs that I learned to use, we base that prescription on simply an observation of a large population. The most common prescription a physician prescribes is "Take two aspirin and call me in the morning."

And the reason it's two aspirin is because we have no idea how much aspirin any one individual should take. But two is generally a pretty good average. And why call me in the morning? Because I have no idea as to whether it will actually work for you. In general, it works, but I need you to call me in the morning.

We are embarking upon an era in which, before I ever give you that drug, I will know whether it will work. And not only will I know, I will know exactly how much you should take.

The problem with drugs is that when we prescribe them based on broad populations and not based on an individual person, some patients in that population will not be getting enough drug, and therefore will continue to have problems. There will be other patients who, perhaps for them, are getting too much drug.

My mother-in-law always told me she was more sensitive to drugs than everyone else. She was right. And now we have the opportunity to personalize those interventions. You'll hear about that with regard to how that actually has occurred with one of the most common blood thinners that we prescribe.

The important corollary to that that I want to stress is the importance of the ability for us to now not only improve quality by getting the right patient the right amount of drug at the right time for the right reason, but also what we'll do in the way of elimination of waste.

By virtue of the fact that we will eliminate the waste of giving someone a drug that was inadequate, or giving them a drug that didn't work or was too toxic, we will have reduced the amount of costs that are involved in our health care system due to inappropriate therapy. And that will enable us to deploy those savings into much more critically important areas of health care that are currently now not able to be fully addressed.

PREPARED STATEMENT

And so Senator Bennett, with that as a broad overview of the importance of why we're here today, I along with you am going to look forward to the specific discussions and examples, and the ability to

answer many of your questions about specific parts and pieces of the initiative.

But suffice it to say we gather today in Utah within the community that we're here to serve to offer an opportunity for a new future in health care that will not only save lives but will also save costs and eliminate waste, and bring us to a period of time where we'll give the right patient the right treatment at the right time for the right reason and get the predictable right outcome.

[The statement follows:]

PREPARED STATEMENT OF ANDREW C. VON ESCHENBACH, M.D.

Good morning. It is a pleasure to join you at this field hearing to discuss one of the FDA's highest priority projects, the Critical Path Initiative. This project has the potential to transform the way medical products in the United States are designed, developed, tested, and used. I want to thank the subcommittee on Agriculture, Rural Development, Food and Drug Administration, and Related Agencies for inviting me to Utah to discuss the benefits the Critical Path Initiative promises to generate for the health of the American public.

I also want to thank you, Senator Bennett, for being the first to provide funding for this important initiative while you served as chairman of the subcommittee during the 109th Congress. Your support of the FDA's public health mission in general—and the Critical Path in particular—reflects your vision for and commitment to better health care for all Americans.

Let me also thank the University of Utah, our hosts today and early collaborators on important work already taking place under the auspices of the Critical Path. University researchers have joined with the Cardiovascular Research laboratory of Intermountain Healthcare in a collaboration with FDA to improve the safe use of a widely prescribed drug. I'll have more to say about that project momentarily.

Holding this event at the University of Utah, under the auspices of the subcommittee and with the cooperation of Senator Bennett, is important symbolically. In today's world of health care and medicine, we are on the brink of unprecedented advances in our ability to predict, diagnose, and treat diseases across the board. But we also face unprecedented challenges in moving those products from the laboratory to the bedside—and in providing access to those treatments.

That's why it's so important to capitalize on the synergies that are created when public health agencies such as the FDA work closely with stakeholders in academic research community, industry, consumer groups and elsewhere to solve problems that affect us all.

The Transformation of Medicine

Close cooperation has become particularly important because what we are witnessing in health care today is the most profound change in the history of medicine. Approximately 100 years ago, our ability to understand disease moved from the macro level, where we were limited to what was visible to the naked eye, to the micro level—when we gained a microscopic view of disease at the cellular plane. But in the last decade or two, we have been able to approach disease at the molecular level, where we now can observe and understand disease as a process.

This is what I have called the "molecular metamorphosis in medicine," because it represents a phase change similar to the transformation of a caterpillar to a butterfly. As a result of this metamorphosis, the future of health care will be no more like its past than a butterfly is like a caterpillar.

The payoff is that, as our knowledge of genetic molecular mechanisms evolves, and our understanding improves, we will be uniquely positioned to develop interventions against disease processes at the molecular level. The potential result is that medicine of the future could be personalized, predictive, preemptive, and participatory.

But there's a problem. Despite an unprecedented increase in funding for biomedical research, both in the private sector and through Federal funding through the National Institutes of Health, this increased research has not translated into many new medical products being available in the medical marketplace. For example, close to nine in 10 pharmaceutical products in phase I testing are never approved for marketing, and half of all phase III clinical trials end in failure. There must be a way to help expedite and simplify this process.

The Critical Path Initiative

That is why in 2004 FDA advanced the notion of focusing on the critical path which medical products must travel, from the earliest stages of development to their use in patients. The Critical Path Initiative is FDA's effort to stimulate and facilitate a national effort to modernize the sciences through which FDA-regulated products are developed, evaluated, and manufactured. The Critical Path provides an essential a tool kit of prospects and initiatives that will enable FDA to make regulatory decisions that will define personalized medicine in this new age of molecular medicine.

To jump start this process, FDA has been working with the academic community, the public, the pharmaceutical industry, and other Federal health agencies to identify the projects most likely to modernize and transform the development and use of medicines. After intensive consultation with many stakeholders, last year we published our "Critical Path Opportunities Report," which details 76 specific scientific projects with great promise for smoothing the path from lab to bedside. Last December, we followed up by announcing more than 40 very promising scientific projects that we have helped get underway.

The Critical Path Initiative presents many major opportunities for improving the process. It includes ways of qualifying biomarkers (which are measurements that can predict or monitor responses to therapy) for in-vitro diagnostics, imaging, and preclinical toxicogenomics. It represents an opportunity to modernize clinical trials to make them more effective and efficient, and we are issuing guidances on advanced clinical trials. It will allow us to harness the potential of modern information technology tools, and it should help us modernize manufacturing by building in quality up front through such systems as quality by design and process analytical technology.

Let me provide a specific example of a Critical Path project that is already underway. It involves work related to cancer, in which FDA is working with a host of other organizations to identify relevant biomarkers and—what is crucial—qualify them for use in the development of medical products.

To achieve these goals FDA and many colleagues established a public-private biomedical partnership supported by the Foundation for the National Institutes of Health. Launched last October, the Biomarkers Consortium strives to accelerate the delivery of successful new technologies, medicines, and therapies to prevent, detect early on, diagnose, and treat a wide variety of diseases, including cancer. Specifically, it seeks to identify biomarkers and develop tests to determine whether a drug is appropriate for an individual patient. It is also working to find markers that will show whether the drug is having the right effect in the patient.

The example of Iressa and Tarceva, two drugs used to treat lung cancer, demonstrates the potential benefits of having appropriate and validated biomarkers. Each of these drugs has had strikingly positive benefits for some of the patients who have taken them, reducing tumors by up to 50 percent and extending life expectancy. Unfortunately, only 10 percent of patients treated with the drugs actually experience these benefits. Researchers have found that the patients who respond to these drugs have a common genetic mutation in their tumors. This mutation can serve as a "marker" to identify the patients who are best treated with these medications. Over time, similar discoveries related to other tumors and drugs are expected to yield a major public health impact—and that is the point of the Critical Path.

A Critical Path Project in Utah

I would be remiss if I did not point out that one of the most promising Critical Path projects is underway right here in Utah. The University of Utah, the Critical Path Institute based in Arizona, and the FDA have established the Cardiovascular Drug Safety and Biomarker Research Program. Its goal is to establish an evidence-based framework for determining the clinical usefulness of cardiovascular biomarkers. For example, in the first of what we hope will be many such projects, researchers in the program are working on ways to establish better dosing of the widely used anti-coagulation drug warfarin. They are attempting to identify the genetic variants in people that determine how they respond to the drug.

This is a medical matter of no small importance to individual patients, because the medical consequences of improper dosing can be severe. Too much warfarin can lead to life-threatening bleeding, and too little can result in equally dangerous blood clots. The overall impact on the U.S. health care system is also profound. Warfarin is the second most common drug, after insulin, implicated in visits to emergency rooms—causing 43,000 ER visits annually.

The goal of this collaboration is to improve our ability to get the warfarin dose right for each patient when they begin treatment with warfarin. Last June FDA and the Critical Path Institute convened a warfarin summit that brought together many

experts in this field, including researchers from the University of Utah. We are looking for ways to find the genetic differences that make patients more likely to metabolize warfarin differently.

As in so many of these Critical Path projects, the goal is to get the right medicine to the right patient, in the right dose, and at the right time.

Conclusion

Let me conclude simply by emphasizing that the sort of collaboration that is occurring every day here at the Cardiovascular Drug Safety and Biomarker Research Program, under the auspices of the Critical Path Initiative, represents the best way, the only way, to take full advantage transformation of modern medicine. It will make innovative medical products available sooner, it will increase our ability to monitor their safe use once they have reached the medical market, it will provide for personalized diagnosis and treatment, and it will introduce great efficiencies while reducing risk.

I should also emphasize that this transformation must take place in the context of a health care system. That's why it is so essential to have a thoughtful national discussion about our health care delivery system, and why it is so helpful to have the constructive engagement of leaders like Senator Bennett.

Finally, I want to commend the University of Utah for adopting this collaborative model. The opportunities—and the challenges—presented by the new age of molecular medicine are so promising and so complex that no one agent can possibly manage them alone. As the body that reviews information about and applications for medical products across the board, FDA is uniquely situated to see the bigger picture. But we are far from having all the answers about how to integrate and capitalize on all the new understandings of medicine at the molecular level.

We share the goal of finding the best way to get promising new interventions to patients. That's where institutions like the University of Utah and Senators like Senator Bennett come in. We need the help, support, and expertise of you and many other partners like you if we are to take full advantage of the opportunities the Critical Path Initiative offers.

Thank you for your time and attention today, and for kindly inviting me to be with you.

Senator BENNETT. Thank you very much. Listening to you talk about "Take two aspirin and call me in the morning," that's trial and error. During the hearing we held on your budget for fiscal 2007 we had an exchange, and you mentioned that the current system of delivering treatment to patients is based on the statistical probability of success.

Obviously it will reduce the cost. But can you talk about the cost of discovering the statistical likelihood? You spend $500,000 to determine that this particular patient——

Dr. VON ESCHENBACH. Yes, sir.

Senator BENNETT [continuing]. Would do better if you had a smaller dose, and then you save 45 cents by giving them a smaller dose. Now, obviously that's absurd. But I'm taking it to that extreme——

Dr. VON ESCHENBACH. Sure.

Senator BENNETT [continuing]. To illustrate the question that I think we need to have addressed.

Dr. VON ESCHENBACH. I think there are two very important aspects of the question that you are addressing. One of which is, first of all, the cost saving not only relates to not giving someone an inappropriate drug. Let me address that first.

We now have, as the most common cancer in the United States and cause of death, lung cancer. More recently a drug was developed to treat lung cancer that virtually was able to have patients who are on their deathbed be able to recover. At least for a period of time. And yet that drug only helped 10 percent of those patients with lung cancer.

It was approved by the FDA because 10 percent is better than zero. And basically there was nothing available for them.

Senator BENNETT. I'm assuming there was no toxic effect on the other 90 percent?

Dr. VON ESCHENBACH. There was really very little in that regard.

Senator BENNETT. Okay.

Dr. VON ESCHENBACH. But what was occurring was the fact that we would be prescribing that drug at approximate cost of $2,500 per month for everyone who fit into that category. So approximately a 100,000 patients would get that drug, when only 10 percent of them were going to actually benefit from it. And we'd be wasting that drug on the other 90,000.

Mark McClellan, who at that time was head of CMS, and I did a back-of-the-envelope exercise that said what we know that about 10 percent of patients who benefit from that drug have a unique genetic mutation in their cancer. And if we only gave the drug to the patients that had genetic mutation, they would be getting the right drug for the right reason.

So if we spent $500 and did a genetic screen on all 100,000, that would cost us money to do that diagnostic test. But then we would only be giving the drug to the 10 percent that actually would benefit from it and we would not waste it in the other 90 percent.

That would result in enormous cost savings, because 90,000 patients would be spared taking a drug that cost about $2,500 per month. That's where we would save money, by not wasting that medication.

Senator BENNETT. I see.

Dr. VON ESCHENBACH. But let me add one other point to that from my perspective. And I don't mean to belabor it. But what was really important in that example I just gave you is we would have not have subjected those other 90 percent of patients to use up the last 6 months of their life getting a useless therapy with a hope that it just might make some difference.

We would be able to allow them to make another kind of choice. Maybe a different kind of drug or a different way to use their time. And that also has to be factored into the equation.

Senator BENNETT. Certainly you are right that the patient psychological benefit is a very important part. But I can figure out that 90,000 times 500 is a lot less than 90,000 times 2,500 a month. Ninety thousand times 500 once?

Dr. VON ESCHENBACH. Once, correct.

Senator BENNETT. Yes, okay. Are there other examples of that same pattern? Where a test could be given to the entire universe that could produce that kind of dramatic cost savings?

Dr. VON ESCHENBACH. They are continuously evolving. For example in breast cancer. Women who have a particular mutation in a gene HER2/neu would then be appropriate candidates for a drug called Herceptin.

You could then know that that drug would be appropriate because it was addressing that particular genetic pathway that was operative in that disease. There are a variety of those kinds of strategies. Looking at estrogen receptors in tumors and deciding which women should or shouldn't get a particular form of hormone

therapy is another way of being able to tailor and make the treatment appropriate for a particular patient.

And what we'll hear today as part of the discussion of critical path is one initiative that Dr. Woosley is particularly involved in, in the development of biomarkers. These markers that will enable us to have the ability to know, in a particular patient, what the right intervention is for them.

Senator BENNETT. Can we go outside the universe of those who are critically ill, like the cancer patients, and say that by virtue of what you are doing in the Critical Path you can have screening activities, genetic screening activities for a wider population?

Dr. VON ESCHENBACH. Yes.

Senator BENNETT. Those who appear fully healthy?

Dr. VON ESCHENBACH. Correct. And when I indicated that one of the promises of this molecular metamorphosis, this movement to this new area, is that medicine would be personalized, which we've been discussing, predictive, which we've also alluded to, and also preemptive.

Preemptive in that we will move to a much more preventative strategy, rather than dealing with an established disease that we recognize when it's fully manifested, to being able to detect susceptibility to certain diseases by virtue of genetic tests or molecular tests and then be able to intervene much earlier, even before someone has the overt manifestation of the disease, is an opportunity to secure health before a disease ever really occurs.

And that's where biomarkers of prediction and interventions—intervention strategies of prevention will become extremely important.

Senator BENNETT. This is probably outside the scope of the original hearing, but as you have this conversation you get into the issue of confidentiality of medical records. Because I can understand a lot of people would be very reluctant to have advance notice, if you will, that they have a predisposition to a particular disease, and have that in a form that might be available to a potential employer.

Say, I won't get the job, even though I'm qualified for it. And in fact, statistically the chances that I will get the disease are sufficiently low that I'm a good risk. But somebody does research on me, I fall into a category that says I have a predisposition to this, that, or the other, and the employer says, I don't want to take the risk.

And as I say, it's outside the scope of the hearing, but it's where we go. Could you talk for just a little bit about confidentiality of medical records?

Dr. VON ESCHENBACH. Yes, sir. I think this is obviously going to be an extremely important challenge that we're going to have to address on a societal level. And I think it's one of the areas where, quite honestly, we're very indebted to the kind of leadership that you are providing by looking at this from, if you will, a health care system approach. And how we appropriately deal with confidentiality.

We have, truth of the matter, been doing genetic testing for decades, if not centuries. We've just called it "family history." Now we're able to take that down to a much deeper level by actually

looking at the genes themselves, rather than just inherited susceptibilities or probabilities.

And how we protect that information and that remains the domain of the individual and not something that then would become publicly available is an important part of how we're going to have to address the health care system.

Senator BENNETT. Let's talk about clinical trials as they go forward. Now, the classic clinical trial, we have a group of blind tests. And they get the placebo and then the others get whatever. Is that process obsolete? Does it need to be changed? Is Critical Path going to have an impact on that?

Dr. VON ESCHENBACH. Yes, sir. One of the important initiatives you alluded to within the 40 that we currently have operative and the 76 that were listed in the opportunities report is our ability to revise and modernize clinical trials and the clinical trial infrastructure.

The traditional clinical trials will still retain an important place in the portfolio, but the portfolio needs to be broadened considerably. There are new kinds of trial designs based on new biostatistical approaches, like Bayesian statistics.

There are what are we call adaptive trial designs in which, instead of testing one drug against another drug or placebo and waiting a long period of time to find out that effect, and then doing another drug and finding that effect, we're able to integrate multiple drugs into a trial using a statistical method that can enable us to learn about each of them simultaneously, and remove some that are not working as well as others. And introduce new ones at the same time.

So it's a rolling trial process that's getting us answers in a realtime, ongoing basis, rather than at an end point that's measured in 5 years or 10 years or 15 years. So we have to change the process to modernize it and use modern tools. And we're also looking at opportunities to change the front end of the process by using, for example, biomarkers, to select patients to go into trials that are particularly relevant for that mechanism.

So it's called an "enrichment" of the trials. You are only testing the drug in the people that are appropriate for that particular drug, rather than in the whole population. So for example if we had a drug for an EGFR receptor mutation that was similar to the one I was talking about, before we wanted to test it we wouldn't test the 100,000 patients with lung cancer. We'd only test the 10,000 that had the EGFR receptor mutation to see if it worked in them. And that's an enrichment trial design.

Senator BENNETT. So the clinical trial gets results faster?

Dr. VON ESCHENBACH. And more precisely.

Senator BENNETT. More precisely. And not to fixate on it, but as an appropriator, at a lower cost?

Dr. VON ESCHENBACH. Yes, sir.

Senator BENNETT. Okay.

Dr. VON ESCHENBACH. And bring those drugs through the process so that FDA would have adequate data upon which to make a regulatory decision. And that would get the drug to patients whose lives are depending upon it much sooner.

Senator BENNETT. Okay, one last question. This all sounds great. I have learned in life that you can have a solution at the FDA headquarters in Washington. You can have a solution passed by the Congress. And then you go out into the world 6 months, a year, or whatever later and nothing has happened.

The water hasn't gotten to the edge of the ditch, to put it in terms that we understand in Utah. How far down the edge of the ditch are we getting with this? Are we seeing this kind of thing beginning to happen and attitudes beginning to change? Or are you running into the force of inertia among medical practitioners?

I've long since learned that inertia is not just a physical force. Inertia is a very strong political force. And it's usually inertia of motion rather than inertia at rest. A bureaucracy in motion can stay in motion and in the same direction.

You are discovering that now, as you take over a major bureaucracy, that it is true of a bureaucracy in a university, or a business, or a church, or whatever. A lot of people are in the inertia of existing clinical trials, and they're comfortable with it.

We're having this conversation about what's being done at the research level. What do you see out at the end of the ditch, is the inertia beginning to change among people who have to deal with this with direct patients?

Dr. VON ESCHENBACH. The inertia is changing very significantly. What I have observed is the fact that, although change is difficult, this change is so profound it's a metamorphosis, in that the future of health care will look no more like the past than a butterfly looks like a caterpillar, it's that profound.

People have come to appreciate that we are in the midst of that change process and it's occurring. And the question still remains what it will be. What it will lead to. But there's no more question about whether it's happening. It's happening.

And I think that points out the reason why it's so important that this hearing is being held here, not in Washington, DC. Because it's happening here. It's happening in this university. It's happening in this cancer center.

It's happening by virtue of the fact that people who will follow me will speak to the collaboration, the cooperation, the integration that's occurring in which people are no longer working in silos, but recognize the importance of interdependence and are creating partnerships, creating alliances. Creating entities, like the C-Path Institute, that are pulling various parts and pieces of this together: The private sector, the public sector, the academic sector.

And that's driving us much more efficiently and effectively through this change process. I don't think it's a question of inertia. I think it's a question of direction or lack of direction as to where and what the future is going to hold.

And I think that's where leadership is going to be required. And that's an appropriate role for an agency like the Food and Drug Administration or the National Institutes of Health not to do it, but to be a part of it and to help guide and direct it.

Senator BENNETT. A trigger—that was going to be my last question, but you triggered one. Are you working with the NIH closely on this?

Dr. VON ESCHENBACH. Yes, sir. One of the important parts of the Critical Path Initiative is exactly the opportunity to work collaboratively and cooperatively with other agencies. We have a biomarker qualification of project within Critical Path that's looking at these biomarkers that will predict disease.

That's being done in collaboration with both the National Institutes of Health and as well with the pharmaceutical and biotechnology industry. And companies are participating in that, sharing data, sharing information about what they're learning and understanding, so that we collectively can accelerate this progress.

Senator BENNETT. Okay, thank you.

We will now take a break while we set up for the second panel. And I have an interview. I'll be right back.

The subcommittee will reconvene. My thanks to the panel for allowing us to have that break. We have roughly an hour left. So I would ask the witnesses to summarize as best they can, so that we can have the kind of exchange that we're looking for.

Again, for the record, the panelists are Dr. Ray Woosley, president and CEO of the Critical Path Institute, an independent nonprofit organization that has a goal of serving as a facilitator among scientists from the government, academia, and the private sector to develop the collaborative research projects that we've been talking about with Dr. von Eschenbach.

Dr. Jeffrey Anderson—raise your hand, Dr. Woosley, so everybody knows who's who. We've got the name cards there, but just to be sure.

And Dr. Jeffrey Anderson. He's the associate chief of cardiology at the LDS Hospital, where he's the co-director of cardiac research and a professor of internal medicine here at the University of Utah. And he regularly teaches medical and premed students, cardiology fellows, and physicians. And because he has nothing else to do, he maintains his own private cardiology clinical practice.

And Dr. Glenn Prestwich, presidential professor and director of the Center for Therapeutic Biomaterials at the University of Utah. He is a member of the Experimental Diagnostics and Therapeutics Program at the Huntsman Cancer Institute. The technology developed from his research has lead to the startup of multiple drug and device companies.

And then Dr. David Jones. He's the senior director for early translational research at the Huntsman Cancer Institute. His research focuses on the identification of new targets for drug discovery in colon cancer. Prior to joining the Huntsman Institute, he was the leader of the drug discovery program for a private company.

You are all involved in Critical Path research. And your research focuses on finding ways to improve the development of medical products. We will turn to you now, each one in the order in which I have introduced you. And you can make your opening statements, and then we'll move to a kind of open discussion.

So we start then, Dr. Woosley, with you.

STATEMENT OF DR. RAYMOND L. WOOSLEY, PRESIDENT AND CEO, CRITICAL PATH INSTITUTE

Dr. WOOSLEY. Thank you, Senator Bennett. Thanks for the invitation to be here and part of this exciting hearing today on a very important topic. In 2005, shortly after the Critical Path Initiative was launched with encouragement and support from FDA leadership, we created this Critical Path Institute, or "C-Path" we call it. And its sole focus is to work with the FDA to facilitate their work on the Critical Path Initiative.

A lot of people don't realize, I don't think, that this response that the FDA has created is really in response to a crisis. A crisis that exists in medical product development today. And it was—you mentioned it earlier in your remarks. I've been looking at the numbers on this. And over the last 10 years, our Nation has spent almost a half trillion dollars on science and research and technology.

A half trillion dollars, yet the number of innovative new products submitted to the FDA have fallen by one-half over the 10-year period. The failure rate during drug development has doubled in that period of time. And every year 3 to 4 percent of new drugs are removed from the market due to safety concerns.

Consider how would the public respond if 3 to 4 percent of airplanes would fall out of the sky within the first year. All of this new science and all this new knowledge and we're less efficient today, not more efficient. We're working harder but we're not working smarter.

The FDA and the industry have come together and they realize that the problem can be explained by a lack of attention to methods development, methods improvement. We've invested billions in basic science, and that's good, but not in applied science.

Applied science is the research on how to better show that a product will be safe and reliable when it's in general use, in any part of the country, in a wide variety of people. We've not developed these new methods to test drugs.

The Critical Path Initiative is all about new methods. It's all about standards for testing and sharing. And sharing sounds simple. However, the pharmaceutical industry is fiercely competitive, and sharing has not been part of its culture.

Also, the FDA can't share. The information it receives is proprietary. Therefore, everybody has been working in the dark. However, the Critical Path Initiative is now creating change. And for the first time ever, industry scientists are sharing their methods.

A year ago C-Path formed a consortium of 160 scientists from industry, from the 16 largest pharmaceutical companies on the globe, to address drug safety. That was 1 year ago. These scientists from these competing companies have been sharing their methods to predict which drugs can cause cancer, which drugs could injure the liver, the kidney, or blood vessels.

They work hand in hand with FDA scientists who serve as advisors, not regulators. On May 7, this group made its first consensus report to the FDA. Recommending new, far more sensitive and specific tests for drug safety. The FDA will now make this information the basis for new guidances for all of the industry to follow.

Clearly, highly-competitive companies can and will work together when the FDA is present. And that's an important caveat. They have to be there for the companies' sharing to be of any value.

Another important element in the Critical Path Initiative was mentioned earlier: Biomarker validation. Well, what does that mean though? Well, "biomarker" is simply jargon. It's a way to measure something that has biological significance and importance.

Blood pressure even is a biomarker, because when it's too high people have strokes. Because the NIH has invested billions of dollars in basic research, we now know how to measure many, many things in biology, and almost all of these things are potential biomarkers.

For example, Dr. von Eschenbach mentioned earlier the HER2/neu. That's a biomarker that can predict which patients with breast cancer will have the best response to the drug Herceptin. Tests like this will make personalized medicine a reality. Without these tests to define our individual differences, doctors will have to continue to practice the one-size-fits-all medicine that we've heard talked about.

Unfortunately though, only a few biomarkers have been validated. That is, they've been proven to the FDA's standards to be clinically reliable predictors. That proof is essential, because sometimes these biomarkers haven't been as reliable as we'd want, and patients have been harmed in the past.

So that FDA proof of validation for a biomarker must be done. Yet we don't know how to do that. That's part of the Critical Path Initiative. How do you validate a biomarker? The FDA has formed—and C-Path have formed an exciting partnership with scientists at the University of Utah, and Intermountain Health Care, and companies in Salt Lake City to develop ways to validate biomarkers more quickly and more efficiently.

That's the goal with the Utah Warfarin Project that Dr. Anderson will tell us about. That project will define the path for development of many of the personalized medicine tests by showing us how to validate these biomarkers.

We believe that this and other Critical Path projects are very wise investments. For example, for less than $700,000 the Warfarin Project, as you stated earlier, will save an estimated $1.1 billion in health care costs, and many lives.

Senator Bennett, we thank you for your leadership and your support of the FDA. There's not a lot of that around these days, as you know. But it's very important today that this groundbreaking work that's being done here in Utah and the other work of the Critical Path Initiative take place. But there's a lot more work to be done.

As you heard, there's 76 projects on this Critical Path Initiative, and we need for those to take place. The rate-limiting step on every one of those projects is the number of FDA scientists available to work with the community, work with people like Dr. Anderson, and work with the people from the pharmaceutical industry, not on their products, but on the process.

PREPARED STATEMENT

Because that's neutral ground, where we all can focus. The work cannot and will not be done without the FDA's active participation.

So I hope we can find the resources to enable the FDA to really be able to be a more effective public servant, the way that Dr. von Eschenbach wants and has as his vision for that agency.

[The statement follows:]

PREPARED STATEMENT OF RAYMOND L. WOOSLEY, M.D., PH.D.

Mr. Chairman and members of the subcommittee, I am Raymond L. Woosley, MD, PhD., President of the Critical Path Institute, a non-profit organization based in Tucson, Arizona and Rockville, Maryland. I thank you for the opportunity to provide testimony today on the FDA's Critical Path Initiative and Personalized Medicine.

The U.S. Food and Drug Administration (FDA), created in 1906, was the first consumer protection agency authorized by Congress. Over the last century, the FDA has protected the U.S. public admirably and set the international standard adopted by most developed nations. In response to tragic drug toxicities, Congress has expanded FDA's authority to require that manufacturers, before marketing a new medical product, must demonstrate its safety and efficacy. Yet, to effectively regulate, FDA scientists must have the necessary expertise and access to the broad scope of scientific information needed to appreciate the strengths and limitations of new advances in biology, medicine, biomedical engineering, genomics, etc. Also, the FDA must have a regulatory framework that can evolve to address the changing complexities of scientific advances. It must be ready and able to accommodate the demands of entirely new scientific fields such as nanotechnology, one of many that will be the basis for new medical products in the future. The current system in which drugs, devices and biologics are reviewed in totally separate and insular centers within the FDA is outmoded. We agree with Commissioner von Eschenbach's vision for the FDA of the future, i.e. one that will better serve the public health by facilitating the development of safer medicines that can be given to the right patient, at the right time and in the right dose.

The Critical Path Initiative

As science has advanced in recent decades, FDA reviewers have asked drug developers to perform more and more testing. However, at the same time, FDA also required older, sometimes outmoded, testing methods. In response, the pharmaceutical industry, unsure what the FDA would require for new drug approval, performed increasingly comprehensive research before submitting applications to the FDA. Development times (time from initiation of testing until submission for approval) have gone from 7 to 15 years and now cost more than $1 billion for a single drug. Despite a 250 percent increase in pharmaceutical research and development investment over the last decade, there has been a 50 percent decline in the number of innovative new medicines submitted to the FDA for review. Last year the number of new drugs approved was the lowest in over a decade. The Nation's investment of over $100 billion last year in biomedical research and development resulted in less than twenty innovative new medications approved by the FDA. Reports from the Congressional Budget Office and the Government Accountability Office agree with the FDA's conclusion that the productivity of the pharmaceutical industry is declining. The ability of this Nation's health industry to create new medical treatments has reached a crisis point.

The Critical Path Initiative began, in concept, in 2003, when the new Commissioner of the FDA at that time, Dr. Mark McClellan, and his Deputy Director, Dr. Janet Woodcock, conducted an analysis of drug development failures and new drug submissions to the FDA. Their conclusions and recommendations appeared in a 2004 report, "Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products." This FDA paper called attention to the rising failure rate of drugs during development which led to a decline in the number of innovative new medical products submitted for FDA review. The FDA concluded that a major cause was the absence of an industry-wide process to reach consensus on which new methods more efficiently and accurately test new products. An important recommendation was a call for the FDA to work collaboratively with scientists in academia and the industry to address the problem. FDA's 2004 report and the subsequent list of 76 projects needed to address the problem have become known internationally as the "Critical Path Initiative."

The FDA, while essential to protecting the public health, has had a negative effect on innovation by adding increasing time and cost to new product development. However, in the FDA's Critical Path Initiative, the FDA has indicated its willingness to help resolve the problem and, as a partner, enable industry to improve the process of medical product development. There has been no effective forum among scientists

from the FDA and the regulated industry to discuss and reach agreement on which testing methods have become obsolete and how they should be replaced.

Yet, FDA is not equipped to accomplish this goal. It has no significant mandate to conduct research nor does it have the necessary funding, staff or resources to do so. Also, the FDA has lacked a platform for effective, early and sustained interaction with academic scientists to better inform regulatory decision making. In January of 2005, The Critical Path Institute or C-Path, was created and operates under a Memorandum of Understanding with the FDA which has liaison representatives on the C-Path Board of Directors (non-voting). C-Path has received Arizona commitments of more than $10 million over 5 years and has seeded five major projects that now have Federal and State funding. One of these awards was made possible by appropriations recommended by this Senate subcommittee (discussed below).

The Critical Path Initiative has transformed the relationship between the FDA and the industry it regulates. Instead of an adversarial relationship, it is now one that better serves the public by enabling FDA and industry scientists to utilize the most modern science in evaluating new products. For example, in the Predictive Safety Testing Consortium created by the FDA and C-Path, 160 scientists from the world's 16 largest pharmaceutical companies for the first time ever are sharing and testing each others drug safety methods. Together, these companies spend an estimated $25 million for in kind research and, under a consortium agreement established by C-Path, openly compare and report findings. FDA is represented at each meeting and is now setting standards for all companies in the world to follow. The companies also share their prior development failures so that others will not make the same mistakes and possibly market unsafe drugs. In this new relationship, scientists from the FDA and its European counterpart, the European Agency for the Evaluation of Medicinal Products (EMEA), participate as advisors and colleagues, not as regulators. This successful FDA-industry collaboration model has been extended to C-Path programs in personalized medicine to develop industry-wide standards for the development of medical diagnostics and treatment of stroke and cancer.

Since the announcement of the Critical Path Initiative, attitudes within the industry and the FDA began changing. For the first time ever, highly competitive companies are sharing their methods and their failures. The FDA and EMEA scientists are meeting with industry scientists to learn and better appreciate the value of the innovative methods the industry has developed. Drug companies and diagnostic companies have agreed to share their methods to measure biomarkers to predict response to cancer drugs. Diagnostic companies are agreeing to validate their diagnostic tests as a step toward setting new standards that will be of value to all companies and patients.

The new collaborative relationships available to FDA scientists have already achieved improvements in the drug development process that will save lives, money and time. On May 7, 60 industry scientists representing the Predictive Safety Testing Consortium, presented their consensus data to the FDA that showed newly developed tests are more sensitive and specific as predictors of drug safety. After the presentation, Dr. Janet Woodcock agreed with their findings and announced that the FDA will now begin to accept the new tests to protect against kidney or liver injury and carcinogenicity. Drugs entering clinical trials and the market will now have much more stringent testing before exposure to humans.

Personalized Medicine: What will it take?

The biomedical community, through increased funding for the NIH, has advanced our understanding of biology, inter-individual differences between people and the pathologic basis for diseases. We are now beginning to recognize the individual biological variations responsible for differences in health and responses to treatment. We are also recognizing that what we have previously considered to be single diseases are likely to be more than one and have major differences between individuals. For example, although many lung cancers may look the same under the microscope, they are actually quite different in their biology and therefore different in their response to therapies. Advances in biomedical science have spawned a new generation of promising targeted molecular therapies and molecular diagnostic tests. Molecular diagnostics have the potential to guide the choice of targeted therapy so that the right patient receives the most effective therapy and at the best dose. However, the potential of this exciting new generation of science is not being realized because therapies and diagnostic tests are not coordinately developed in the pharmaceutical industry and they are not reviewed and regulated in a coordinated fashion by the FDA.

For over two decades, genetic tests have been reported in the medical literature demonstrating their ability to predict patients' response to drugs. However, they are not becoming part of the routine practice of medicine. The major reasons relate to

the barriers to commercialization of the diagnostic tests. One of those barriers is the lack of standards for such tests and concerns about the cost and predictability of a path toward FDA approval of the tests. In order to define the standards and demonstrate the path, C-Path developed a partnership between the FDA and a team of scientists at the University of Utah and Intermountain Healthcare. The goal is to evaluate genetic tests for their ability to predict safer and more effective doses of the anticoagulant warfarin (Coumadin®). Warfarin is a generic drug widely prescribed as a blood thinner to prevent dangerous blood clots. The optimal dose varies from patient to patient and may range from 1 mg/day to 40 mg/day. If the dose is too high, the patient may have serious bleeding and conversely, if the dose is too low, the patient may suffer a stroke or embolism. In both these situations, death can rapidly follow. The University of Utah is performing the clinical study and C-Path will evaluate the methods used in the study to assure the FDA that the results of the trial can be used to write dosage recommendations for warfarin based on genetic testing. A recent Joint Report from the Brookings/American Enterprise Institute concluded that, if the Utah study is successful and its results incorporated into the practice of medicine, 85,000 serious bleeding events and 17,000 strokes can be avoided annually and $1.1 Billion in healthcare costs will be saved each year.

For the promise of personalized medicine to be realized, diagnostic tests that can predict an individual person's response to therapy must reach the market and become routine components of therapy. One of the factors that has limited widespread application of personalized medicine test biomarkers is the lack of a clear path at FDA for approval for such assays. By working with the FDA and the University of Utah, the warfarin genotyping project is expected to form a path to FDA approval and would aid pharmaceutical and diagnostic companies as they develop new drugs and diagnostics. The new process created by the FDA for this project could serve as a model pathway for other personalized medicines.

The FDA of the Future

In order for the FDA to efficiently regulate the development of new biomedical products, it needs many more opportunities to interact with cutting edge scientists. We believe the model that C-Path has developed with its Cardiovascular Safety Biomarker project is an excellent example of how best to address this need. Under a cooperative agreement with the FDA, C-Path has identified the leading scientists in the Nation with the expertise needed to develop new genetic tests to guide the initial dosage selection for warfarin.

I recommend that the FDA be given the resources and staff to form collaborations to more aggressively work on the Critical Path Initiative. We have found the concept of a "critical path public/private partnership" to be an effective mechanism to leverage FDA's limited resources to maximum benefit. C-Path's success in bringing the Federal regulators and the regulated industry together results from its scientific credibility and its financial neutrality. This neutrality is only possible because of the unrestricted funding that it receives from the Arizona community to pay for the operating costs and to seed the Institute's programs. Congress has recognized the value of neutrality, transparency and mutual oversight when industries work with Federal agencies on "process improvement." In the past, Congress created Sematech for the computer chip industry, the National Center for Food Safety and Technology for the food industry and others. Public-private partnerships like C-Path can serve as the neutral third party for the health product industry and the FDA and can fill a major unmet need for the Nation by making it possible for biomedical innovations to reach the public with greater speed and safety.

Senator BENNETT. Thank you very much.

Dr. Anderson.

STATEMENT OF DR. JEFFREY L. ANDERSON, ASSOCIATE CHIEF OF CARDIOLOGY AT THE LDS HOSPITAL, CO-DIRECTOR OF CARDIAC RESEARCH, AND PROFESSOR OF INTERNAL MEDICINE AT THE UNIVERSITY OF UTAH

Dr. ANDERSON. Good morning. I also extend my thanks to Senator Bennett for his long-time support of medical progress to provide all of us with better health care. For your particular interest in this initiative and for organizing this field hearing. Obviously I'm biased, and I appreciate it's here in Salt Lake City.

I also express appreciation to the FDA for its leadership in this initiative that I believe can dramatically improve health care.

Well, we've heard a lot about cancer. And the other big gorilla, if you will, in health care is cardiovascular disease. Heart and blood vessel disease. It is a leading cause of morbidity and mortality. Almost a million Americans die each year of cardiovascular disease.

And the importance of family history has really been emphasized here in Utah in a classic study that showed that in general about 14 percent of us have a family history of early heart disease. But if you have heart disease yourself, the risk is 50 percent. And if you have early-onset disease, three-quarters of patients will have a family history. And, of course, it's genetics that transmits that family history more than anything.

And genetics not only determines predisposition and susceptibility to disease, but also how we respond to diet. What we eat. Environmental pollutants, that unfortunately we're getting more of in the air here in Salt Lake City even. And medications, which we are increasingly using, as we've heard, in large numbers to prevent and treat disease.

Now, we've found so far in our work that genetics of coronary disease is complex, thanks to some support from NIH. And we'll continue that effort. But pharmacogenetics, which is the application of genetics to the optimal use of pharmaceuticals, is more straightforward and I believe will likely lead the way in the initial application of genetics to the prevention and treatment of cardiovascular disease.

And I'd like to return to an example that's been alluded to that in just a minute. But just for a moment who you're hearing from here, I've had the opportunity to see medicine from several different perspectives: As a student, as a resident trainee, as a servant in the Public Health Service for a while, and a bench researcher in the National Institutes of Health for a season, to an FDA volunteer on the Cardiorenal Advisory Panel, and later as its chair a decade ago. And even for a brief time as an executive director of the Cardiovascular Pharmaceutical Development Program for new drugs for a large international company.

But for most of the last 30 years I've had the wonderful and varied experience of being an academic cardiologist, including teaching, clinical and translational research, applied research if you will, but most importantly serving my patients as their physician and cardiologist. And one of the challenges that I certainly can attest to as a physician is that treatment is indeed geared to the crowd, if you will, whereas I only deal with individual patients.

When I am paged to our hospital's laboratory for a critical case, I can anticipate that quite often it will be a case for an out-of-range for prothrombin, which is a measurement of the effectiveness or activity of the common blood thinner warfarin or coumadin, the brand name as we've heard about. Of course putting that patient at high risk. And I always break out in a little bit of a sweat, knowing that that patient for the next few days, until we get that back to normal, is going to be at higher risk.

And that's just one prominent example. Side effects from several other drugs again occur in individuals and has already been stated. This is a daily challenge. If we knew in advance, it would be a much better situation. So individualizing selection, and dosing, and

medications to individual patients based on genetics, I concur with the others that have spoken, is a prime opportunity for better medicine for the future.

Now, warfarin has been mentioned, and it's certainly a prime target for this initial application. It's prescribed to over 2 million Americans for prevention of clotting disorders. And unfortunately, warfarin has a very narrow therapeutic range of balance, a tight rope, between too much causing bleeding problems or too little allowing clotting problems to occur.

And so clinical management has been, as you've heard, very difficult. And that's because there's tremendous interindividual variability in warfarin metabolism, leading to unpredictable and up to 20 full differences in the maintenance dosing requirements. And right up until now we've only been able to determine that by trial and, unfortunate error, and frequent blood testing.

In recent years it's been exciting to discover two genes that are responsible, together with age, sex, and weight, for over half of the variability. This tremendous variability. But clinical application of genetic testing has lacked. And it's really minimal at the present time.

One of the reasons is we don't have good clinical controlled trials that prove the benefit. What's the cost of this? What are the tradeoffs? So recognizing this need, and with encouragement and support from the C-Path Institute and also with support from FDA in this critical pathway, we undertook a prospective randomized trial just a little over a year ago with a rapid genotyping assay that allows us to get back information in about an hour. Again which is a critical, I think, component of applying this.

And that has already been published recently. And I'm pleased to announce that we've just completed this first major randomized trial in 200 patients. We're involved in the analysis. And we hope by the end of the month to submit this for review and we hope publication in a major medical journal.

We think that this will be of great value to the National Institutes of Health that we've been collaborating with in setting up a major multi-institutional and much larger trial that we hope will finally validate this approach, and allow it then to be applied nationally to these 2 million patients who are begun and have treated on warfarin.

Senator BENNETT. Can I interrupt you there?

Dr. ANDERSON. Yes, sir.

Senator BENNETT. We need to move along.

Dr. ANDERSON. Okay.

Senator BENNETT. If you have another major point——

Dr. ANDERSON. Shall I just summarize?

Senator BENNETT. If you would, please.

Dr. ANDERSON. I was just going to say that this is, of course, just one example of many other drugs that we have in mind. And so let me just conclude then by saying that I think the C-Path Institute is a prime example of how a neutral party can partner with FDA. And how important the C-Path initiative is to bring together these many parties that I have mentioned.

PREPARED STATEMENT

But this early promise, of course, needs ongoing support to really, I think, achieve the true potential of this approach. And the result could and should be a major advance in health care for all Americans, individualized to their personal needs. And I thank you for your time and attention.

[The statement follows:]

PREPARED STATEMENT OF JEFFREY L. ANDERSON, M.D.

Good morning. I am pleased to join you at this field hearing to provide my personal insights relevant to the Critical Path Initiative. I will testify that this high priority FDA project has great potential to facilitate the much-needed transformation of the way medical products in the United States are developed and applied and to take advantage of the vast potential of modern human genomics. I want to thank the subcommittee on Agriculture, Rural Development, Food and Drug Administration, and Related Agencies for inviting me to participate as a physician and medical scientist as well as a concerned and interested citizen.

I extend my thanks as well to Senator Bennett, for his long-time support of medical progress to provide better health care for all Americans, for his particular interest in this initiative, and for his organization of this field hearing.

As a graduate and faculty member, I wish to recognize the University of Utah, for its support of genetic medicine in general and its particular interest in the Critical Path Initiative. I express appreciation to the FDA, for their stimulating leadership role in a collaborative project that can dramatically improve the health of our own and especially future generations. Finally, I wish to particularly recognize Dr Raymond Woosley, whose passion for this initiative has led to his formation of the not-for-profit C-Path Institute, a vehicle to assist in applying the Critical Path Initiative to the development and application of pharmaceuticals and new medical devices. Our own research has been honored to serve as his cardiovascular clinical collaborators over this past year. This role has been facilitated by financial support from a grant awarded by FDA and funded by Congressional mandate. I will comment on the return for this investment later.

The Genetics Revolution and Its Implications for Healthcare.—Completion of the Human Genome Project has launched medical science into the "Post-Genomics Era",[1] [2] yet application to clinical medicine is still embryonic. The human genome consists of 3 billion base pairs of DNA, comprising an estimated 20,000–25,000 genes ("loci of co-transcribed exons") arranged on 46 chromosomes (22 autosomal pairs plus XX or XY). The human genetic map is remarkably constant, with inter-individual differences occurring on average at only 1 in 1000 base pairs, yet this 0.1 percent variance accounts for genetic-related differences in both normal human traits and disease predisposition.[3]

Overall, about 10 million relatively common polymorphisms in single nucleotides (SNPs) have been found within the human genome; perhaps 100,000 have functional consequences (are non-synonymous). Normal diversity-determining variants can be postulated to number a few thousand, common disease-determining genes and genes affecting the metabolism of our major drugs, perhaps a few hundred. Thus, despite substantial genomic variability, the search for the genetic underpinnings of common diseases and patient interactions with treatment, although enormously challenging, is believed to be a realistic possibility. This search has struggled through an embryonic stage, and the true potential of genetic medicine is as of today almost completely untapped. Its successful application will require a cooperative, societal commitment, including full participation by government, academics, industry, and public interest groups at many levels.

The Health Burden of Cardiovascular Disease and the Contribution of Genetics.—Cardiovascular diseases (CVD) are the leading cause of morbidity/mortality in the United States and the Western world.[4] Coronary artery disease and its major clin-

[1] Lander ES, Linton LM, Birren B, et-al. Initial sequencing and analysis of the human genome. Nature 2001;409:860–921.

[2] Ventner JC, Adams MD, Myers EW, et-al. The sequence of the human genome. Science 2001;291:1304–51.

[3] Guttmacher AE, Collins FS. Genomic medicine—a primer. N Engl J Med 2002;347:1512–20.

[4] Thom T, Haase N, Rosamund W, et-al. Heart disease and stroke statistics—2006 update: A report from the American Heart Association Statistics Committee and the Stroke Statistics Subcommittee. Circulation 2006;113:85–151.

ical sequel, myocardial infarction, represent the major contributors. The importance of family history was emphasized in a large University of Utah database study, which found a positive family history of CAD (onset in first degree relative at age <55 in men, <65 in women) in only 14 percent of the general population, but 48 percent among those with CAD and 72 percent (almost three-quarters) of those with premature onset of disease.[5] Twin studies and other family history evidence suggest that heredity and environment contribute approximately equally to CAD disease etiology. The genetic contribution to CAD is believed to be multigenic and complex.[6]

It has been said "genetics loads the gun, and environment pulls the trigger". Genetics not only determine disease susceptibility but also the response to the diet, environmental pollutants, and medications, ever increasing in number, used to prevent and treat disease. Given the complexity and slow progress in determining genetic susceptibility to CVD, pharmacogenomics, the application of genetics to the optimal use of pharmaceuticals, can lead to the way in the application of genetics to prevention and treatment of CVD.[7]

Insights from a Personal Journey through the Healthcare System.—My personal journey through medicine has included many stops along the way after medical school, including residency training in internal medicine and speciality training in cardiology, bench research at the National Institutes of Health, with an appointment in the Public Health Service, many years in the practice of cardiology, volunteer service for the FDA on its Cardiorenal Advisory panel, which I also chaired, and even a brief adventure in industry as Executive Director of Cardiovascular Clinical Research for an international pharmaceutical company, as a Cardiology Division Director, and, as a practicing cardiologist seeing patients. For 28 of the past 30 years, I have particularly enjoyed the varied experience of academic cardiology, including teaching, clinical and translational research, and, importantly, serving my patients as their physician and cardiologist. This varied experience has brought me an appreciation of the wonderful potential of modern medicine but also pointed out its challenges and deficiencies.

One of these challenges is that our treatments are geared to the crowd, whereas I deal only with unique individuals. I am on call 24 hours a day for my own patients and cross-cover for my academic partner, Dr. Brent Muhlestein, and share Wednesday call with colleague, Dr. Robert Fowles, for the large Utah Heart Clinic and the cardiology needs of the LDS Hospital Emergency Ward. When paged to the LDS Hospital laboratory for a "critical value" when on call, I can anticipate that an "out-of-range" value for the common blood thinner "warfarin" (or Coumadin®) is often the reason, putting that patient at high risk for a bleeding event. Rare to more common side effects of other drugs, again which occur in individuals, is a daily challenge. Individualizing selection and dosing of medications to individual patients, based on genetics, is a prime opportunity for better medicine for the future.

Pharmacogenomics: Its Bright Promise for Now and the Future.—Currently, all patients are treated with the same drugs and doses, yet safety and efficacy vary depending on genetic background. The promise of pharmacogenomics is to customize therapy by determining in advance who will be responders to usual dosage (e.g., ≈60 percent of a patient group), responders at higher dosage (e.g., ≈10 percent), responders at lower dosage (e.g., ≈15 percent), non-responders (who need alternative therapy, e.g., ≈10 percent), and those at adverse risk (idiosyncratic or toxic, e.g., ≈5 percent).[7] Pharmacogenetic applications represent a very promising first major venture into the application of genetics to personalized medicine, and a golden opportunity for efficient use of resource and research efforts today.

Pharmacogenetic-Guided Dosing of Warfarin: Applying Genomics to Medicine Today.—A prime target for the initial application of pharmacogenetics to broad application in CV medicine is the orally active anticoagulant warfarin. Warfarin is prescribed to over 2 million patients in the United States for prevention of clotting disorders ("thromboembolic disease") associated with such conditions as atrial fibrillation, prosthetic heart valves, orthopedic surgery (e.g., knee or hip replacement), venous thrombosis, and pulmonary embolism.

Unfortunately, warfarin has a narrow therapeutic index, and clinical management is difficult. Recurrent thromboembolism, due to inadequate anticoagulation, and se-

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[5] Williams RR, Hunt SC, Heiss G, et-al. Usefulness of cardiovascular family history data for population-based preventive medicine and medical research (the Health Family Tree Study and the NHLBI Family Heart Study). Am J Cardiol 2001;87:129–35.

[6] Hopkins PN, Hunt SC, Wu LL. Family history and genetic factors. In: Wong ND, Black HR, Gardin JM, eds. Preventive cardiology, a practical approach. New York: McGraw-Hill; 2005:92–148.

[7] Anderson JL, Carlquist JF, Horne BD, Muhlestein JB. Cardiovascular pharmacogenomics: current status, future prospects. J Cardiovasc Pharmacol Therapeut 2003;8:71–83.

rious bleeding events, due to excessive anticoagulation, are relatively frequent. Substantial inter-patient variability in warfarin metabolism leads to variable (up to 20-fold) and unpredictable dosing requirements.[8] Oral anticoagulation trials for non-rheumatic atrial fibrillation have determined the optimal range of the blood test, prothrombin international normalized ratio (INR), to be 2–3 with ratios <2 increasing thrombotic events and those >4 increasing hemorrhagic events and with a marked increase in intracerebral and other serious hemorrhage at INRs >5.[9] [10] Careful clinical follow-up and frequent blood testing for INR are required to ensure effective anticoagulation while avoiding over-anticoagulation and serious bleeding events.

Variants in 2 genes affecting warfarin metabolism (CYP2C9, VKORC1) recently have been discovered by us and others to conjointly determine stable warfarin dose.[11] [12] Together these genotypes plus certain clinical characteristics predict approximately one-half of inter-individual dose variability.[11] [12] These recent studies suggest that CYP2C9 and VKORC1 genotyping may be of substantial interest for clinical application. Indeed, the Clinical Pharmacology Subcommittee of the FDA Advisory Committee for Pharmaceutical Science has recommended CYP2C9 and VKORC1 genotyping to optimize warfarin dosing. However, clinical application has been limited, in part because of cumbersome assays and the lack of clear demonstration of an incremental advantage on outcomes of genotype-guided dosing algorithms by prospective, controlled trials.

Recognizing this need, and with encouragement and support from the C–Path Institute, and made possible in part by FDA grant funding, we undertook a prospective, randomized pharmacogenetic (PG)-guided dosing study. A rapid turnaround (clinical "real-time") genotyping assay, one pressing need holding up clinical application, already has resulted from these efforts.[13] Using this assay and a predictive algorithm, developed from recent work by our group, we have completed the first major randomized study of PG-guided dosing, "CoumaGen", in 200 patients initiated on warfarin therapy, and plan to analyze and submit our written report to a major clinical journal this month for review and publication. These results should play an important role in the planning of a much larger, multicenter study to be sponsored by NIH, to validate the PG-guided approach to warfarin dosing in clinical practice. The safety impact of this single effort in pharmacogenomics could be substantial.

Making Cardiovascular Drugs Safer A Pharmacogenetics Initiative of Highest Priority.—A next step with warfarin is to apply routine genetic testing for dose-selection within the IHC system, involving several thousand patients per year, and measure its impact on healthcare outcomes. If positive, these efforts could rapidly be expanded to regional and national networks with large potential health care benefits.

Warfarin represents only one of a multitude of cardiovascular drugs that we have identified, together with FDA input, as potential targets for pharmacogenetic research and future clinical application. To investigate genetic associations requires DNA samples and patient information. Our research group has collected and banked blood for serum samples and DNA, together with family histories and complete medical records, from 15,000 patients undergoing coronary angiography over the past 12 years. Information on over 2 million patients in the Intermountain Healthcare Electronic Database also is available, with appropriate approvals and safeguards, for expanded research efforts. Intermountain Healthcare (IHC) has a world-class computerized information system that allows for tracking of deaths, other cardiovascular events, and adverse drug events. In addition, the FDA has an Adverse Event Reporting System (AERS) for signal detection of interest. Working in collaboration with FDA in a C-Path oriented project would allow us to determine safety signals of interest, perform retrospective and prospective surveillance studies within

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[8] Voora D, McLeod HL, Eby C, Gage BF. The pharmacogenetics of coumarin therapy. Future Medicine 2005;6:503–13.

[9] Hylek EM, Skates SJ, Sheehan MA, Singer DE. An analysis of the lowest effective intensity of prophylactic anticoagulation for patients with nonrheumatic atrial fibrillation. N Engl J Med 1996;124:970–9.

[10] Oden A, Fahlen M, Hart RG. Optimal INR for prevention of stroke and death in atrial fibrillation: a critical appraisal. Thrombosis Research 2006;117:493–9.

[11] Carlquist JF, Horne BD, Muhlestein JB, et al. Genotypes of the cytochrome p450 isoform, CYP2C9, and the vitamin K epoxide reductase complex subunit 1 conjointly determine stable warfarin dose: a prospective study. J Thromb Thrombolysis 2006;22:191–7.

[12] Sconce EA, Khan TI, Wynne HA, et al. The impact of CYP2C9 and VKORC1 genetic polymorphisms and patient characteristics upon warfarin dose requirements: proposal for a new dosing regimen. Blood 2005;106:2329–33.

[13] Anderson JL, Hinz WA, Clarke JL, Et-al. A rapid (1 hour) genotyping assay for polymorphisms affecting the dose-response to warfarin therapy. J Am Coll Cardiol 2007.

the Cardiovascular and General IHC databases, identify patients with events, and, with consent, obtain DNA samples and test for candidate genes or do genome wide genetic scans to identify adverse event-related genetic causes. Several specific projects already have been identified as of potential interest and importance to national CV health:

—New or worsened heart failure after therapy with anthracycline chemotherapies (doxorubicin, daunorubicin, idarubicin), imatinib, and trastuzumab
—Rhabdomyolysis from statins
—Angioedema and ACE inhibitors
—Variability of clinical response to and safety of beta blockers
—Pharmacogenetic basis for sporadic long QT syndrome (causing serious, unexpected heart rhythm disorders).
—Genomics and adverse response to QT prolonging drugs
—Confirm (or refute) linkage of CV adverse events with certain drugs, including the coxibs (Vioxx, etc), the thiazolidinediones (Avandia, etc.), and the GI motility agent Zelnorm, and, if confirmed, identify a genetic basis.

In anticipation of these projects, we have performed a feasibility study on the IHC database and have identified to date:

—2,300 out-of-range INR for patients taking warfarin (40 percent of all INRs!).
—Developed a method to link databases in the Utah system to other systems so that out of range prothrombin time (INR) values can be validated as a surrogate for adverse events due to warfarin.
—Conducted baseline analysis of the monthly rate of INR out of range values to enable power calculations for future intervention studies
—23 subjects with anthracycline related heart failure
—27 patients with ACE inhibitor-related angioedema.
—102 with rhabdomyolysis while taking statins.

Implications for the Future of Medicine and why the Critical Path Initiative is Important.—In the post-genomic era, the central role of genetic-environment interactions on human health and disease is unquestioned. However, genetic application in the day-to-day practice of cardiovascular and general medicine is to date minimal. A paradigm shift from "treating the crowd" (generalized medicine) to "treating the individual" (personalized medicine) seems to be the clear and single path to a better era of health care in the future. While the complex role of genetics in polygenetic diseases such as CAD is being sorted out, the application of pharmacogenetics to medicine is approaching "prime time".[14] To make application a reality, however, will require a clear societal commitment, for many ethical and practical issues, as well as scientific ones, must be overcome. The FDA's Critical Path Initiative currently stands out as the single most important way forward. The C–Path Institute is a prime example of how a "neutral party" has partnered with FDA and the C-Path Initiative to bring together Government/Regulatory, Industry, Academics, and Public Interest groups, to overcome barriers, and to address common problems for the public good. This early promise of C-Path is a direct result of Congressional support; its ongoing success and true fruits can only be realized with expanded support and with a long-term commitment. The result could and should be a major advance in health care for all Americans, individualized to their personal needs and characteristics.

I thank you for your time and attention today, and for inviting me to be with you.

Senator BENNETT. Thank you.

Dr. Prestwich.

STATEMENT OF DR. GLENN D. PRESTWICH, PRESIDENTIAL PROFESSOR AND DIRECTOR, CENTER FOR THERAPEUTIC BIOMATERIALS, UNIVERSITY OF UTAH

Dr. PRESTWICH. Thank you. I'll do my best to move things right along. Senator Bennett, again thank you, with the other panelists, for the opportunity to present our testimony. I think I'm here because I'm an academic who's also an entrepreneur, and so I want to present the point of view that that, that that embodies.

I have started companies that develop tools for pharmaceutical drug discovery. And in fact have been part of discovery of anti-can-

[14] Roden DM, Brown NJ. Pre-prescription genotyping: not yet ready for prime time but getting there. Circulation 2001;103:1608–10.

cer and anti-infective drugs. In addition, more recently I've been involved with starting companies that make medical devices for wounding—for improved wound care. And also now for tissue engineering, which is part of cellular therapy, which will be one of the new regenerative medicine techniques of the future.

That's a separate issue with the FDA, and I won't go there, because we're going to focus on, on the personalized medicine focus. But let me, let me convey my impressions in the area of new biomarkers and disease models, which is one of the Critical Path six priority areas for improving health care in the United States.

So specifically my testimony will address the use of tissue engineering technologies to improve both upstream and downstream potential to unplug the drug discovery pipeline. What we've been talking about is a pipeline that's plugged. The water is not getting to the side of the ditch.

So let's—I'm going to look at it at two different areas: upstream and downstream. So upstream in the drug discovery pipeline, I think, as Dr. von Eschenbach points out, we need to develop safer treatments faster and more cost effectively. I've got some ideas on that.

Second, at the downstream end we need to see how tissue engineering technologies not only can cure people better, but maybe they offer a better potential for individualizing—individualization of treatment options. And I have an example that I'd like to present in that regard.

We haven't talked much about the actual cost of individual drug development. Right now in the pharmaceutial industry the estimate is about $1.2 to $41.4 billion to develop a new drug entity, and it takes about 12 years to accomplish that.

The problem is that only one out of seven or eight compounds gets through the pathway—through Phase III clinical trials and gets approved for market. That means that seven out of eight, or six out of seven, depending on which numbers you believe, are failing.

Of those, at least a quarter of them or more are failing because of hepatotoxicity. That's toxicity to the liver. And that's happening only in large-scale Phase III studies. Right now you can only find it out that way.

So one of my feelings for unplugging the drug discovery pipeline would be to improve the rate at which we can eliminate kidney toxic or liver toxic compounds early in the drug discovery pipeline, upstream, before they get into the very, very expensive and potentially life-threatening Phase III studies.

This can be accomplished or is now being worked on in research laboratories translationally with tissue engineering technologies. So, for example in my lab, we develop materials that allow us to culture small versions of the human liver that are functional. And we can grow those small liver organoids and test drugs, thousands—hundreds of thousands of them in a couple of weeks against a functioning version of the human liver.

Well, that's one way to do it. That would be the high industrial-strength version of it. But what you really want is that construct to represent a functioning liver in a rodent model. So you take a rat and you take out the rat's liver and you put in a human liver.

Now you've got an organism that's going to be your best equivalent of a human. Which is that it has the liver metabolism of a human. It's got all the circulation. Things are moving around. Things are getting broken down. You can find some of those things that are called "idiosyncratic toxicities," which are compounds that become toxic after the liver activates them.

So it's being able to find those toxicities that normally you wouldn't find until you were in a large human population. We can find those earlier. That's going to unplug the pipeline at the upstream end. Make it safer, quicker, cheaper.

So coming to personalized medicine, that's still sort of genetic, right? Because it's upstream. So my take on personalized medicine is summarized in what I call my slogan. Which is it's all about "Drug and Dosage—Getting it Right for Dick or Jane." If you can't distinguish between Dick and Jane, then you can't get it right for either the drug or the dosage.

So really there are two levels. Everything that we've heard about so far is at the genetic level. That's the gene. Those are the programs, the blueprints that encode everything that we're made out of. But I want to address a different area, which is the phenotype.

The phenotype is who we actually are. It's what's actually built from those blueprints. It's not the stuff that's on the architect's desk, it's the stuff that you're actually walking through the door of when you move into your home. So I think that the phenotype, the individual phenotype, is equally important for looking at opportunities in personalized medicine.

And so let me talk about one specific example in the idea, the concept that I have for individualizing anti-cancer drugs. So the technology at one of my companies here in Salt Lake City, Glycosan, consists of an injectable material that you can load up with cells. And so we've done this now, not just for engineering of livers, and kidneys, and bone repair, and things like that, but also for engineering tumors.

So this seems like the wrong thing to do. Growing a better cancer seems like a really dumb thing to do. But in fact it's not. It's not so dumb, because most of the anti-cancer compounds in the clinic right now will fail. And they'll fail because they've only been tested in animal models. And animals are really, really bad predictors of what's going to happen in a human.

So we want to put human tumors in a more human context. And you want to be able to go further than that but test a specific drug for Mrs. Anderson or Mrs. Jones and make sure that, that patient gets the right drug.

So here's how we've used this model. Let's take breast cancer. So we've injected breast cancer cells. And it could be Mrs. Jones' or Mrs. Anderson's own tumor cell that we inject in the real setting of this. We take those cells and inject them in the mammary fat pad. That's essentially the breast-like tissue of the mouse. And then we grow tumors. We grow breast tumors.

Now you have mice that are growing—in this case, it could be Mrs. Anderson could have her own set of mice, and Mrs. Jones could have her own set of mice. And then you would go with a particular set of drugs. Mrs. Jones has failed cisplatin, her drug—her

cancer is resistant to cisplatin and Taxol and doxorubicin. Now what are we going to try?

Well, you can go to the pharmacy and pull out a whole bunch of things and try one after the other or try them all at once on Mrs. Jones. But that's using the patient herself as the experimental animal. Why not take cancer out of the patient, put it in the animal. And then use animals, with that patient's own cancer, determine which is going to be the best treatment for that particular patient.

So that hasn't been possible in the past because everything has used tumor cell lines. And most of them don't work very well anyway. But we can personalize that by taking Mrs. Jones' and Mrs. Anderson's tumor cells, put them into a mouse, couple of mice. Try this set of drugs with that mouse, try this set of drugs with that other mouse.

And pretty soon you say, this mouse is living; the tumors are regressing, let's go with that combination. That would take about 4 weeks. And then you have 4 weeks in the cancer decision-making process as to when you want to decide what to give as the next therapy.

So rather than drone on about that, that's my feeling for a downstream approach to phenotype-driven personalized medicine.

Senator BENNETT. Okay.

Dr. PRESTWICH. So in my concluding remarks——

Senator BENNETT. Right.

Dr. PRESTWICH [continuing]. I want to emphasize that academic research, to be translated to the clinic, has to be commercialized. And so the academic entrepreneurial investor interface is extremely important. And we must recognize that we need to build things, not for our own publication lists, but for patients and physicians who are going to use things in the end.

PREPARED STATEMENT

And so this Critical Path Initiative is part of that process to get translational research more emphasized and more on the minds of academics so that we actually do translate things—to individualize therapies. And to use the best tissue models, the best animal models, the best safety testing that we can possibly do to get better, faster, cheaper drugs.

[The statement follows:]

PREPARED STATEMENT OF GLENN D. PRESTWICH

Executive Summary

The FDA Critical Path Initiative has identified "Better Evaluation Tools—Developing New Biomarkers and Disease Models" as one of the six priority public health challenges to be considered as a major opportunity in improving health care in the United States. This topic includes biomarkers that could facilitate the development of personalized medicine strategies. It also includes the development of more predictive preclinical models for drug efficacy and safety. My testimony addresses strategies and technologies in tissue engineering with both upstream and downstream potential. First, at the upstream end of the drug discovery pipeline, improved models based on tissue engineering can help the pharmaceutical industry discover safer treatments faster and in a more cost-effective manner. Second, at the downstream end of the pipeline, tissue engineering offers the potential for individualized treatment models for drug selection using biopsy samples. Such methods would allow a physician to customize a treatment before administering it to a patient.

What is the Underlying Question?

One of the six priority public health challenges for improving health care in the United States was identified in the FDA Critical Path Initiative as "Better Evaluation Tools—Developing New Biomarkers and Disease Models." This topic includes the discovery and use of genetic and phenotypic biomarkers that could facilitate the development of personalized medicine strategies. It also includes the development of preclinical models for drug efficacy and toxicology that have better predictive value for clinical usage.

The fundamental problem is the long time required and the high cost of drug discovery. A second problem that exacerbates this fundamental problem is the high failure rate in Phase III clinical trials. As a result, drug discovery strategies are overly conservative in the molecular targets explored and are designed to identify "blockbusters"—single drugs that treat millions of patients and yield over $1 billion annual sales. The blockbuster paradigm is fundamentally at odds with the concept of personalized medicine, which strives to achieve a patient-oriented treatment for individual molecular disease pathologies.

In the testimony below, I describe how strategies and technologies in tissue engineering possess both upstream and downstream potential. First, at the upstream end of the drug discovery pipeline, improved models using tissue engineered human organoids can make safer treatments available more rapidly and in a more cost-effective manner. Second, at the downstream end of the pipeline, tissue engineered constructs made using a patient's own normal and diseased cells can be used to individualize treatments by taking the guesswork out of drug selection. Such methods would allow a physician to customize both the drug and the dose before administering it to a patient.

Why are so few new Drugs Reaching the Marketplace?

Currently, it costs some $1.2 billion some 12 or more years to bring a new molecule from the laboratory bench to the bedside. Only one drug candidate in seven succeeds in the expensive and time-consuming Phase III clinical trials. A significant fraction of these failures are due to liver toxicity, and occur after hundreds of millions of dollars have already been spent. Reducing failure at this stage could substantially lower the overall costs of drug discovery. It has been said that, "The holy grail of the [pharmaceutical] industry is to be able to predict [drug] toxicity from a cell culture." However, current methods for identifying hepatotoxic drugs are far from achieving this goal. Measuring cytotoxicity in cultured hepatocytes can predict some instances of acute toxicity in the clinic, but this does not take into account the many drugs (~40 percent) that fail because they are metabolized in vivo to toxic species. This idiosyncratic toxicity cannot currently be detected until large-scale Phase III clinical trials.

New tissue engineering technologies, including those developed in my laboratories, offer opportunities for in vitro and in vivo liver toxicology models by culturing human liver cells—from the immature hepatic stem cells to mature hepatocytes—as organoids. The key is to recapitulate the cellular microenvironment experienced by normal cells as they normally grow and mature in the adult human liver. The ability to grow metabolically competent engineered liver tissue is an important "growth industry", and the Utah technology allows growth of engineered human liver constructs for toxicological studies.

One step beyond ex vivo organotypic models is the development of whole-organism pharmacokinetic and pharmacodynamic models. Since drug metabolism in rodents and humans differ dramatically, one solution could be the production of mice with engineered human livers. This moves from metabolic profiling in an ex vivo human organoid to the study of how the metabolites from the organoid interact within an intact organism. Perhaps such a system might further reduce Phase III failures.

What is Personalized Medicine?

My philosophy on personalized medicine is summarized in this slogan: "Drug and Dosage—Getting it Right for Dick or Jane." There are two levels at which personalized medicine can be approached: genetic and phenotypic. Most discussions now focus on the genetic level. A person's genome is the unique blueprints that encode the building instructions for all the proteins in his or her body. However, genes are not inevitable destiny, because how these blueprints are read changes as we develop and as the environment changes. Thus, arguably more important for personalized medicine, is the phenotype of an individual. This is who we actually are—which proteins have been made correctly (or incorrectly) based on those instructions. Others in this hearing will testify about the importance of using genetic markers in optimizing drug selection and drug dosing. My testimony will focus on the phenotypic approach to personalized medicine.

The tissue engineering technology developed at the University of Utah allows a vision for personalized medicine in which tissue biopsies can be utilized for the determination of drug safety and efficacy for a specific patient. This takes the more general approach used above for reducing the number of hepatotoxic drugs reaching Phase III clinical trials and makes it personal. We envision that an array of potential pharmaceutical intervention options, could be pre-evaluated for safety and efficacy ex vivo using a patient's own normal and diseased tissues. The next section describes one such approach to downstream personalized medicine.

Individualized cancer treatments: downstream personalized medicine

Current animal xenograft models used to evaluate new anticancer therapies are limited to a small number of "generic" cancer cells lines, fail to mimic the complexity of the normal human disease, and poorly predict clinical outcomes. Our technology has generated an injectable, in situ crosslinkable biomaterial called Extracel™ that can be used to deliver and grow cancer cells in vivo by a technique we call "tumor engineering." We have shown that we can engineer breast, colon, pancreatic, and ovarian cancer in mice by injection into the mammary fat pads, the colon, the pancreas, and the ovaries, respectively. These engineered tumors are important new tools to study cancer biology, invasion and metastasis, and to investigate new therapeutic and diagnostic protocols. In fact, we have recently used our model to validate the safety and efficacy of a new anti-cancer drug invented at the University of Utah. This small lipid molecule turns off a specific cell signaling pathway and causes tumors to regress. In addition, it simultaneously suppresses metastasis, and shows a very large therapeutic window.

To individualize the tumor engineering protocol, we would take a breast tumor biopsy from a patient—perhaps pre-treatment, or possibly after cancer has recurred—and obtain a heterogeneous pool of cells that would be suspended in Extracel™ and injected in mice to give two to four breast tumors. In the same mouse, we would also inject normal non-cancerous breast cells in Extracel™ into the fat pads on the other side. We might generate twelve mice per patient. Approximately 2 to 4 weeks later, large tumor masses would have formed on one side, and small normal breast organoids would be formed on the other side. Then, a variety of treatment options could be evaluated in order to identify a patient-specific optimal therapy. This could be a new drug candidate, a new combination of existing drugs, or a new treatment regimen. In this model, the patient herself is not the test animal. Instead, a patient-specific surrogate allows multiple options to be explored before treating the patient. This is what I consider to be the ultimate in downstream patient-specific therapy.

Conclusions

No product of academic research reaches a patient unless it has been the focus of an intense research and development effort by a for-profit company. This development effort includes a rigorous evaluation of safety and efficacy by the FDA. To be successful, products must focus on the unmet needs of patients and their physicians, who are the ultimate customers of the research efforts funded by the National Institutes of Health and funding sources. I believe that it is both the obligation and responsibility of researchers to adjust our research priorities to meet the needs of our customers. In an analogous context, the customers of the FDA are also the patients and their physicians. Thus, it is my strongly-held opinion that the FDA, too, must continuously evolve to meet the changing needs of its clientele. The critical path initiative is indeed part of the process of change, embodying when appropriate the best tissue models, animal models, safety testing, and individualized therapy options that new technologies can provide.

References

Portions of this testimony are excerpted from:

—Prestwich, G. D.; Liu, Y.; Yu, B.; Shu, X. Z.; Scott, A., 3–D Culture in synthetic extracellular matrices: New tissue models for drug toxicology and cancer drug discovery. Advances in Enzyme Regulation, 2007, in press.

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Biographical Sketch

Since 1996, Dr. Glenn D. Prestwich is Presidential Professor of Medicinal Chemistry at The University of Utah, with adjunct appointments in the Departments of Chemistry, Biochemistry, and Bioengineering. He received a B.Sc. Honors (1970), Chemistry, California Institute of Technology and a Ph.D., Chemistry (1974), Stanford University. Previously, he was Professor of Chemistry and of Molecular and

Cell Biology, Stony Brook University (1977–1996) and Director, NY State Center for Advanced Technology in Medical Biotechnology (1992–1996). He received Alfred P. Sloan Research and Dreyfus Teacher-Scholar Awards, the 1998 Paul Dawson Biotechnology Award of the American Association of Colleges of Pharmacy, and is a Fellow of the American Institute for Medical and Biological Engineering. He received the TIAA–CREF Greater Good Award (2006), was a Utah Business Magazine Health Care Hero (2006), and was awarded the Governor's Medal for Science and Technology (2006). He has directed two Centers of Excellence: the Center for Cell Signaling (1997–2002), and the Center for Therapeutic Biomaterials (2004–2008). He co-founded and was former CSO of Echelon Biosciences, Inc (1997–2003) and Sentrx Surgical, Inc. (2004–2005). He is currently Senior Scientific Advisor, Carbylan BioSurgery, Inc. (Palo Alto, CA) and a co-founder and CSO for Sentrx Animal Care, Inc. and Glycosan BioSystems, Inc. Dr. Prestwich has published over 590 technical papers, patents, and book chapters, and has trained over 71 graduate students and 55 postdoctoral associates.

Senator BENNETT. Thank you very much.

Dr. Jones.

STATEMENT OF DR. DAVID A. JONES, SENIOR DIRECTOR FOR EARLY TRANSLATIONAL RESEARCH, HUNTSMAN CANCER INSTITUTE

Dr. JONES. Okay. Good morning. And thank you, Senator Bennett, for the opportunity to share my view on personalized medicine and help contribute to the discussion of the Critical Path Initiative. I think we've heard today already, and I'll give a unique sort of personal perspective about the rich history of genetic research that the University of Utah enjoys.

I left a major pharmaceutical company about 10 years ago in order to come here for the opportunity to juxtapose genetic-based science with drug discovery. And I realize, believe it or not, that I thought I could achieve this kind of match in my research better in an academic setting than I could at a major pharmaceutical company because, in many ways, of this inertia that we talked about a little bit, being resistant to this kind of approach in the pharmaceutical industry.

And so I have been here for 10 years at the Huntsman Cancer Institute. And the Huntsman Cancer Institute is following in the footsteps of the broader university community in trying to understand what are the underlying genetic causes of the various kinds of cancers. And if we can understand that, we can think about better therapies to give to these patients with a defined genetic cancer.

And one of the resources that we have—and I think that I'll just point this out so that I can make a point that this is already happening—is personalized medicine. It's coming whether we want it or not. And we just need to prepare for it.

And one of the examples that I take advantage of all the time as a scientist is that the Huntsman Cancer Institute operates what are called "high-risk clinics." And that means we know about the people in the State of Utah who carry specific genetic mutations that predispose them to specific kinds of cancers.

We know about the people in Utah who have a clear genetic inheritance of cancer, even though in some cases we don't understand the underlying genetic basis. And these patients are invited to come in to these high-risk clinics for screening.

And in this case we're going back and thinking about prevention by bringing them in. In the case of colon cancer, which is my spe-

cialty, they can undergo colonoscopy on a regular basis, and we can think about heading off cancer prior to its onset.

One of the things that we're able to do of course then is that we can study these patients when they come in. We can get their tissues. We can look at what's wrong with the tissues. We can think about new ways of approaching it.

If you think about a specific gene that has mutated in colon cancer right now that causes 85 percent of colon cancers, the options for these patients who are high risk, meaning they inherited the mutation in this gene, is to have their entire colon removed when they're in their 30s or early 40s.

And so we are very interested now in saying, look, we have this genetic resource. We understand who is at risk. We can now understand the underlying biochemical problems and think about new therapies that we can apply to them. And of course the idea would be to go back and use these same patients that we used as the guiding principle for developing the drug and put that drug back into those patients.

So our overall goal is to try to improve both diagnostics and treatment. And I think that it sort of points to what I would say needs to happen in the drug discovery and approval process. In that science really has moved in the last 10 years from one investigator studying one process for his entire career, her entire career, to using technologies that allow us to assess globally what's wrong in disease. We know, we can give you the molecular recipe for a colon cancer now by looking at all genes in the genome.

And I think that my view of what needs to happen in order to facilitate this is that the drug discovery process has to go from being what historically is a more linear process. Meaning that the target and the discovery of the drug is often uncoupled from understanding toxicity of the drug and understanding the patient population. And we need to have a much more broad overview of the process from beginning to end.

The clinical trialist has to understand the molecular process. The people who worry about toxicities need to think about what are the potential toxicities up front, when the target is going to be discovered. And I think therein we can achieve some balance and savings by simply getting smarter about which ones are going to go forward from the very beginning, based on a strong genetic rationale.

And then I'll just bring up one other point that I think I haven't heard yet, and I think this cooperation between academia, the FDA, and industry, a coordination of that could certainly benefit from.

And that is that when you're talking about genetic therapies, and you're talking about therapies that are going to go into specific populations; those populations, believe it or not, become a commodity. Pretty soon you have a very limited number of patients who are eligible for an EGF receptor trial, or an APC colon cancer trial.

And I'll just give you a specific example, is that we were interested in testing a new drug for a specific genetic form of colon cancer several years ago, only to learn that virtually every person diagnosed with this genetic mutation in the country was already on another trial for a drug that was not targeted for that specific genetic mutation in the first place.

PREPARED STATEMENT

So I would just bring up that one of the things that we need to think about in order to achieve this is to change the paradigm and say, look, we can't be running trials for drugs that aren't tailored toward the genetic defect if there are trials that could be run that are.

And so I just will conclude again and say thank you for the opportunity. And we look forward to hearing more.

[The statement follows:]

PREPARED STATEMENT OF DAVID A. JONES, PH.D.

Good morning. I would like to first thank Senator Bennett for inviting me to participate in this discussion of the Critical Path Initiative and the potential for improving the process of delivering innovative new therapies to the American public.

The University of Utah stands on a rich history of scientific research aimed at defining the genetic causes of human disease. In continuing this tradition, research at the Huntsman Cancer Institute aims to enhance our knowledge of the genetic basis underlying cancer development. Our goal is to apply this knowledge to improve cancer diagnosis and treatment. The broad research community has made remarkable progress in defining the genetic causes of cancer and the medical community is now within reach of transforming new discoveries into new therapies. Indeed, we have heard of examples today that exemplify the promise of this approach. The Huntsman Cancer Institute is committed to improving patient care by tailoring therapeutics that serve to correct or exploit the specific underlying causes of cancer. In this regard, genetic research in a number of our laboratories has defined promising new targets for drug development and we are currently working to identify novel agents that will affect these specific processes. We believe this approach will improve treatments, maximize safety and reduce costs.

Realization of the benefits offered by personalized medicine research is not without challenge. Success in these efforts will require new initiatives aimed at streamlining the drug testing and approval processes. The Huntsman Cancer Institute applauds the goals of the Food and Drug Administration's Critical Path Initiative, which seeks to "stimulate and facilitate a national effort to modernize the scientific process through which a potential human drug, biological product, or medical device is transformed from a discovery or "proof of concept" into a medical product." We believe that the promise of personalized medicine can benefit from a new level of cooperation between academia, industry and the FDA. For example, coordinated efforts between those identifying new opportunities, those developing innovative therapeutics and those engaged in definition of patient populations and clinical trial design could help to ensure rigorous scrutiny and focused application of emerging therapies. We believe this type of coordinated effort can be facilitated by a strengthened dialogue between the private and public sector.

The Huntsman Cancer Institute is committed to forwarding the cause of cancer research and treatment. We are eager to engage in any activities that will make the process of medical product approval "faster, safer, smarter".

Senator BENNETT. Thank you very much. We've got about half an hour now to interact with each other. Let me kick off with one question that occurred to me in your testimony, Dr. Woosley. You say 3 to 4 percent of the drugs are being withdrawn. They got through the approval process. They obviously had some significant benefit. And then they got withdrawn.

And my question is, could the drugs still be available with the benefit if, by virtue of what we're talking about here with Critical Path, you say, okay, we now know not to give the drug to X, Y, and Z, but they still should be available for A through W?

Dr. WOOSLEY. Absolutely. That is absolutely right, Senator. That is the goal. The goal is not to take the drugs off the market. Because we know they can help people. The goal would be to know enough about the problem early enough to find out how to deal with the problem.

And there are genetic tests today that could predict, we believe, most of the drug toxicities that are out there, but they haven't been validated yet. And there are a lot of consortia biomarker groups around the country working to do that. But we don't have the standards set yet.

So the Critical Path is all about setting the standards for how those biomarkers, how—if we—for example, we know that Vioxx——

Senator BENNETT. Vioxx is a poster child for this.

Dr. WOOSLEY. Exactly.

Senator BENNETT. A lot of people benefitted from Vioxx.

Dr. WOOSLEY. A lot of people still need Vioxx. And it would be great to be able to make it available to them. About 6 percent of people don't metabolize Vioxx and most of the other drugs like it. They don't burn it up. They've got higher blood levels. And they're probably the ones at risk for toxicity. But we haven't proven that.

If we could go—and we know that this is a genetic norm—it's not an abnormality. Six percent of normal people just don't burn up, don't metabolize Vioxx. We could today, the genetic test is marketed and approved by the FDA today, but the insurance companies don't pay for it because they haven't gone to the next step to show that Vioxx patients with that genetic abnormality should never get the drug.

So yes, the problem as I see it is we look for toxicity too late. We need to have an active surveillance system that the agency is working on right now. They've been having meetings and learning how to do active surveillance, because it's not being done anywhere else in the world right. But that's what we need. To be able to find these problems early enough and then deal with them.

Senator BENNETT. Dr. von Eschenbach, do you have a method in the FDA whereby you could put Vioxx back on the market?

Dr. VON ESCHENBACH. Exactly in line with what Dr. Woosley was alluding to, Mr. Chairman. If we can define the exact right population for whom that drug is appropriate, we could provide that drug on the market with those specific labelling indications for that use and that use only.

Senator BENNETT. And Dr. Prestwich, could you figure out a test that people could go through? Or is this more easily solved than the kind of human test you're talking about?

Dr. PRESTWICH. No. As with, as with what Dr. Anderson was talking about, they're actually testing for—not so much for the gene, but they're testing for the activity of the enzyme. So it's the gene product, it's the phenotype.

And so both phenotypic and gene—both protein and gene tests could be done. And I think the combination of the two is what I would be moving towards to suggest.

Senator BENNETT. Have at each other now. I've exhausted my capacity to sound intelligent on this issue.

Dr. WOOSLEY. Well, I was fascinated by Dr. Prestwich's techniques that he's developing. I think that they're absolutely what we need. We need to be able to bring together engineers. I think that one of the real problems of the pharmaceutical industry for many years is it's been too isolated, and they've not brought in the other technologies like engineering and tissue engineering.

We've been looking at rats and mice by themselves, and being able to look at human tissue allows us to look at these differences. And as he pointed out, it's not just human tissue, it's the person's tissue. And that's challenging.

And, and I guess I would ask Dr. von Eschenbach, is the agency ready to accept new methodologies that bring in engineering and bring in tissues from an individual? I mean, they're used to looking at mean populations. I think I know the answer to this.

Dr. VON ESCHENBACH. Well, the answer is no. We're not prepared for this new future and this new reality. And part of what I have been so appreciative of is the support that we have received from the committee in being able to address the kind of investment that will be required to modernize the FDA and modernize its regulatory processes.

It is a broad, comprehensive effort that will bring these new tools of science and technology into the regulatory process. It is beyond just the issue of genomics. It involves proteomics and ultimately metabolomics, or how people metabolize these various drugs.

And we are taking a full life cycle approach. Traditionally one might think of the FDA as a place where someone brought an application for a drug, we made an analysis and a decision, that drug went out into the market, and then we waited to hear something about it.

We now are going to be engaged in the full life cycle. Proactively engaged in the development of those drugs so we get it right at the beginning. The best way to provide something for a patient is to build the quality in on the front end. Use these tools to not just determine whether the drug is going to be effective when it gets into Mrs. Jones, but whether it's also going to be safe when it gets into Mrs. Jones.

That needs to be done on the front end. We need to have the processes that also enable us to stay engaged even after that drug goes out into a large population. Because we'll never be able to know everything that we need to know in the context of a clinical trial. Which is just a selection or a subset that we hope reflects the large population, but it rarely ever does.

And we now, because modern tools of science and technology, information technologies, are available today that weren't even available 10 years ago, we now have the ability to start staying engaged after market, in active surveillance. To be getting signals, not when someone actually has a heart attack from a particular drug, but when they actually start showing metabolic or biochemical changes in markers that would predict, if they continue on, that will be a problem.

And that will enable the FDA to provide for the American people a system that protects and promotes their health by being engaged in getting them the products. And enable them to use those products, whether it's a drug, or a vaccine, or whatever.

Dr. WOOSLEY. Could I ask the Commissioner to elaborate a little bit? I've heard him talk before. And as I was listening to Dr. Prestwich, you know, he's going to bring in your door a tissue. And he's going to ask, Which door do I go in? Do I go in biologics, or do I go in devices, or do I go in the drug door?

And I know you've talked a lot about and I was really impressed with the concept of the laptop. Do you remember that conversation?

Dr. VON ESCHENBACH. Well, I think what this new era is defining for us, Senator Bennett, is that what patients need and what they want are not drugs or biologics. What they want is a solution to their problem. And invariably a solution will require a combination or an integration of things.

If we look at somebody that has hair of my color, we don't take one drug every day. We take lots of drugs every day. Some for our cholesterol, some for our blood pressure, whatever. The point is that solutions will involve an integration of these drugs, biologics, and devices.

And that's going to require a transformation in terms of how does FDA make regulatory decisions when someone brings us a solution which is perhaps a product that is a combination of a drug or biologic device.

And you and I have had private conversations about the importance of addressing this, even as we see on the horizon the benefits of progress that's being made in a field like nanotechnology. That it's going to be bringing to us entirely new realities that FDA has not had to address previously.

The industries and others are going to have to come together, much like the computer industry did, in realizing that there will always be drug companies and vaccine development companies. Just as there are always companies that make hard drives, and CD–ROMs, and microprocessors. But what the patient wants is a laptop. Or what the consumer wants is a laptop.

And how they put those parts and pieces together in a way that shared intellectual property that allows for interoperability is a challenge that we're going to have to work through with the industry as they come together to share and integrate their parts and pieces. Not only the products but the, but the data, the knowledge about these products.

Dr. Woosley has been leading an initiative to help drive this, where pharmaceutical companies are coming together and they are actually sharing data that they have in their possession about their various products as it relates to their toxicities or their side effects.

And so that they can learn from each other, and not inadvertently go down a road to create something that would wind up being catastrophic and somebody else already knew that. And we can cut that off. That's part of the leadership that I think that FDA has to provide.

Senator BENNETT. You talk about the laptop. Let me give you an aphorism that comes out of the business school. We've got one businessman there. But this is one of the first things you have to learn in business. Nobody wants a quarter-inch drill. What he wants is quarter-inch holes.

And that is exactly the basic concept here. Nobody wants a quarter-inch drill. What they want is quarter-inch holes. Nobody wants a television set. What they want is the Jazz game, and the "Super Bowl", and "Seinfeld", and "MASH", and whatever else.

So a lot of people spend all of their time working on quarter-inch drills. And then somebody else comes along and says, "I can give you a quarter-inch hole cheaper, better, and cleaner."

And they say, "Well, what's wrong with my drill?"

"Nothing is wrong your drill. I don't want a drill. I want a quarter-inch hole."

Okay. Any other back and forth? Yes, sir.

Dr. ANDERSON. Well, I don't know if this is the right group to bring it up to, but I had a little experience in industry. And one thing industry wants to do is give the same drug in the same dose to everybody and have them take it every day.

Senator BENNETT. Yes.

Dr. ANDERSON. And so at least when I was there, there was some resistance——

Senator BENNETT. There's an industry that did that, and it's called the tobacco industry.

Dr. ANDERSON. How can we involve industry more fully? What will they see in this new era of genetics? Now, I think one answer might be that maybe they can keep their Vioxx on the market if they can get rid of safety. But there must be a balancing act that we can encourage them to go along with us in this new initiative.

Dr. WOOSLEY. One of the aspects of that, just quickly add, is the compensation today. We pay for drugs. We pay a lot for drugs. But we don't pay for the diagnostics yet. So I know CMS is very much interested in personalized medicine. And we've got to find a way to reimburse for the diagnostic. And I think that, that will help a lot.

Dr. VON ESCHENBACH. The other thing I would comment on that regard is that the other lesson to be learned as far as this new future that I've been describing is this fact that they're going to have to rethink market share. One would consider developing a drug for lung cancer because there are a lot of lung cancer patients around, for example. And they're looking for a blockbuster. A drug that's going to be the be all and end all.

But the fact of the matter is, that one of the most important drugs that was developed for cancer based on an understanding of mechanisms, the fact that in order for a tumor to grow it had to have blood supply, and so one drug was developed to block the development of those blood vessels to feed the tumor.

That drug, those angiogenesis inhibitors, actually are having your greatest impact on wet macular degeneration of the eye. Totally, completely different disease, but same mechanism. Same molecular mechanism. So now you have a drug that actually is going to be able to capture parts and pieces of a variety of diseases.

We're seeing that even in some of the cancer drugs. I alluded to the poster child for chronic myelogenous leukemia. Turns out that that drug has dramatic effects in a tumor you wouldn't have even imagined would be like a leukemia; a sarcoma of the stomach.

And so we're going to see different kinds of models. And there are going to have to be different ways of the companies rethinking their development strategies along lines of mechanisms, not along the lines of anatomic expression of the disease.

Dr. JONES. So, since I am one of the people that had big pharma experience, it is exactly this blockbuster mentality that we needed one drug to cure all cancers that got me to leave the industry and come here.

Because the first question that I was always asked when proposing a new scientific project was, What is the market share of this drug if you're able to, to do it? And if the answer is, Well, I can treat 10 percent of the patients, the answer—the response was, Next. Right? And who's got another idea.

And so I think what they really are going to need is to see some successes. What they see out there are drugs like antihypertensives and other drugs that are prescribed widely and generating a lot of money. This promise of these targeted therapies really being profitable for pharmas is really just a promise right now.

And I think that examples that come through ought to start to change their attitude and say, look, I can live with 10 drugs that are effective in 10 different ways rather than one that I need to treat all of them with. And so I think it's just time in one level, but they will need some coaxing. And hopefully we can help facilitate that.

Dr. WOOSLEY. I think the industry people tell me now that they have come to realize that, for example a company that markets a drug for lung cancer where it only works in 10 percent of the people. They've gotten FDA approval, but they can't get doctors to use it when they know that 9 out of 10 won't respond. So they're running into this. And they're now actually ready to sit down and talk about a diagnostic.

Dr. PRESTWICH. So I just wanted to echo what Dr. Jones said with the blockbuster mentality. And if we have a faster, safer way to unplug the pipeline at the upstream end, then the economics will not dictate that you have to go for a blockbuster.

And the importance of that is that you can now start going after not only lesser, smaller populations, but other targets. There are 100—I think there are 220 or 240, I forget the number, of compounds currently in use for treating diseases. And they target less than 5 percent of all the potential drugable pathways that could be used to ameliorate or cure a given disease.

So by opening up, by unplugging the pipeline and making it, you know, a $100 million to get a drug through the clinical trial process and approval process, that all of a sudden gets rid of the blockbuster mentality. You've got a lot more targets. A lot more drugs.

And now you are able to do a personalized medicine because you have a much bigger palette of colors. It's not, it's not like you've got red, white, blue, and green anymore. You've got, like they say on the computer screen, millions of colors. That's really what we need.

Dr. WOOSLEY. Could I put a plug in for the FDA's budget, though? Because for that to happen the industry has to know that there's a path at the FDA that they can follow. The FDA put out a guidance on drug diagnostic co-development almost 2 years ago. It's still a draft guidance. They haven't had the staff to address that.

You know, it's part of the Critical Path Initiative and I compliment the Commissioner for all they're doing, but I think he can't tell you how understaffed and under resourced they are at the agency. But I talked to these people when I was at Georgetown. I helped train most of them. And I know that they are good people trying to do a good job under horrible circumstances.

You know, the FDA is in Montgomery County, Maryland. The school board budget for Montgomery County, Maryland is bigger than the FDA's budget.

Senator BENNETT. But the school board doesn't have to go through OMB.

All right. You're not going to complain about their request?

Dr. VON ESCHENBACH. No, sir. But I wondered if there were other questions that people had that related to this idea of the Critical Path. Because one of the things that I have found in discussing Critical Path is how easy it is for people to be confused about what it actually means.

And I think it's been expressed here today in a variety of ways. But at the heart of it is the fact that, as Ray has just pointed out, there is enormous opportunity for us to bring to health care an entirely new way of providing solutions to patients for the diseases that plague them.

It will also help us to bring in this whole area of diagnostics integrated with the therapeutics. And we're even coining new terms like "theranostics," and the idea that we'll have the ability for patients to have a tool that will enable us to understand the disease process and the person with that disease process that's coupled with the intervention.

And that is opening up another important area that FDA has to address. We have not embarked upon the regulatory process around diagnostics and the integration of those diagnostics with therapeutics. We've tended to think in terms of drugs, and biologics, and devices. And now we're thinking in terms of these new platforms of diagnostics. Whether they're genomic, or proteomic, or other technologies that are going to emerge.

And it adds to Dr. Woosley's point that for FDA to be responsive to this new reality of these new challenges and these new opportunities it will need to be a different FDA than in the past. And I really appreciate this opportunity to help try to explain a small portion of that at this very important hearing.

Senator BENNETT. Let's get into science fiction for just a minute. As I listen to this, right now when a baby is born you can determine blood type. And that's important. And when I'm in the Army they put a dog tag around my neck that has my blood type on it. And there's no stigma attached to the fact that I'm A, and you're B, and he's O, and whatever. Indeed, it's important information.

Suppose, Dr. Prestwich, you take an 18-month old child in, take some tissue and hand the parents, 2 weeks later, a profile. The child will carry that profile through his or her whole life. Becomes part of the medical history. Goes in for checkups, whatever. We need to worry, when you're a teenager you might have an onset of diabetes. Can we do some things to worry about that? You have a predisposition to breast cancer. You—so on and so forth.

Purely science fiction, purely down the road, but react to that. How, how possible is that at some point in the future?

Dr. PRESTWICH. It's not really science fiction. We have, we have essentially the capabilities of doing all of that now. Getting information is easy. Knowing what to do with the information and having something to do it with is the problem.

And so we're doing so many prenatal and post—and immediately—postnatal tests already. There are some perfectly good examples of phenylketonuria, PKU. You can diagnose that very early during pregnancy. And still the only thing that we can do when the kid is born is change the child's diet. There's nothing else that we can do for a PKU kid except make sure that the kid gets the right diet.

So it's not the information. We've got way too much information, in fact. And way too few tools with which to act on the information. And derth of reimbursement mechanisms to pay for many—those that are too expensive don't get paid for.

Senator BENNETT. Now, I object to your statement "We have way too much information." You don't have it properly organized.

Dr. PRESTWICH. Yes. We have lots of information.

Senator BENNETT. That's our fault.

Dr. PRESTWICH. Yes.

Senator BENNETT. That's the kind of thing we need to work on. But a child goes to school, and we have programs whereby everybody—at least according to the law, has to have an inoculation. We've stamped out smallpox. We've stamped out polio.

The kinds of things that I used to experience as a child are just medieval to my children and grandchildren. Like when I describe the Public Health Service coming by and putting a sign on our house that says "Quarantined" and nobody can go in and out.

That's was just great, because one of my brothers or sisters would get chickenpox and none of the rest of us had to go to school for 2 weeks or whatever until that sign came down.

Dr. PRESTWICH. Yes.

Senator BENNETT. Could we get to the point where as a child goes to school, in addition to all of the inoculations and shots, he gets this kind of profile that becomes his. And then from that information, as further research is done later on some physician will say, "Let me see your profile. We can do this"?

Dr. PRESTWICH. So that is science fiction. It would be very nice well, science fiction is science fact of the future.

Senator BENNETT. In other words, it is scientifically possible——

Dr. PRESTWICH. Yes.

Senator BENNETT [continuing]. But financially and administratively right now?

Dr. PRESTWICH. Precisely. So what you are describing is what we were able to do with infectious diseases in the past. Now, to be able to do that with genetic disorders is a taller order, and I think that's what we're talking about now.

Senator BENNETT. Yes.

Dr. VON ESCHENBACH. I just want to add one other dimension to this. In "FDA" that first word is "food." And just to limit it to the issue of nutrition and, as you are describing, the ability to understand an individual even from the time of birth and through childhood and what to do during that period of time.

One of the very important opportunities that will emerge out of this new era of molecular medicine, if you will, is our better understanding of the role of nutrition. Because, in fact, the most significant biologic response modifier we put in our mouth every day is not the drug we take, it's the food we eat.

And over a period of time we do not understand nutrition from a molecular perspective as well. And yet we are able to start to do that in ways that we can begin to tailor, for individuals, things that they should be doing even as it relates to the role of nutrition as a way of ensuring, preserving, and enhancing health later on in their life.

And I think even, from the point of your colon cancer, we understand that fiber, soluble fiber, may be beneficial for colon polyps. But in fact it does depend upon what your genetic polymorphism is for some of those colon polyps, because in certain circumstances soluble fiber may actually be worse rather than better.

So personalized nutrition as well as personalized medicine is perhaps more science fiction today than some of the things we've been talking about, but I think will follow on very rapidly, Mr. Chairman, as an important part of what we will do with that child when we fully understand what that child's potential is in the future.

Senator BENNETT. Yes.

Dr. ANDERSON. Just to add on, from a cardiovascular point of view one of our concerns is though we've made progress over the last 50 years in reducing, decade by decade, the risk of cardiovascular disease, we're now worried it's going to start going back up again because we're getting fatter as a Nation.

And that leads to more diabetes, high cholesterol, high blood pressure, sleep apnea, just a host of syndromes. And one of the problems is we need to solve this thing about the balance between nutrition and activity. And it's not just everybody that's getting fatter, but particularly a certain subgroup that seems to be prone to it. As you say, that's involved with genetics.

I've noticed, interestingly enough, just recently a gene, the FTO gene that's been identified as if you have this gene in two—a double dose, that you weigh 8 pounds more. That doesn't sounds like a lot, but if you add a few of those genes together that all adds up.

And so that could well be part of this as well. Not only the drugs we take, as you say, but what kind of diet you should be on, and how much exercise you need, and—begin a training program early in life.

Senator BENNETT. Okay. Any last words? We're getting close to the witching hour, but if you have some really important gem you want to share with us, please go ahead.

All of your written statements will be included in the record. And we will keep the record open for a week or so if you have some absolute brain flash that you say, "I wish I had said that," you can submit it to us in writing and we will include it in the record.

CONCLUSION OF HEARING

Senator BENNETT. Dr. von Eschenbach, thank you for coming to Utah. I think you see that we have reason for you to come here. And thank you to the panel that has been assembled.

Again, my thanks to Senator Kohl, the chairman of the subcommittee, who has approved this field hearing and made it possible for us to come. The subcommittee is recessed.

[Whereupon, at 11 o'clock, Friday, June 1, the hearing was concluded, and the subcommittee was recessed, to reconvene subject to the call of the Chair.]

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