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WORKSHOP ON

INNOVATIVE SYSTEMS FOR DELIVERY OF DRUGS AND BIOLOGICS:

SCIENTIFIC, CLINICAL, AND REGULATORY CHALLENGES

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TUESDAY, JULY 8, 2003

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The workshop was held in the Grand Ballroom of the Bethesda Marriott, 5151 Pooks Hill Road, Bethesda, Maryland, at 8:00 a.m.

PRESENT:

DAVID FEIGAL, JR., M.D., M.P.H., Center Director, CDRH

MARK McCLELLAN, M.D., Ph.D., Commissioner, FDA

ROBERT LANGER, Ph.D., Massachusetts Institute of Technology

DAVID C. KLONOFF, M.D., U.C. San Francisco

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PRESENT (Continued):

JONATHAN B. KRUSKAL, M.D., Ph.D., Harvard Medical School

RICHARD E. KUNTZ, M.D., M.Sc., Harvard Medical School

AJAZ HUSSAIN, Ph.D., Nektar Therapeutics

CHET LEACH, Ph.D., Nektar Therapeutics

BILL VAN ANTWERP, Ph.D., Medtronic MiniMed

KEVIN C. SKINNER, V.M.D., Genzyme Corporation

JONATHAN S. KAHAN, ESQ., Hogan and Hartson, L.L.P.

KEITH SMITH, Becton, Dickinson, and Company

CHRISTINE ALLISON, M.S., RAC, Eli Lilly and Company

JOHN JENKINS, CDER

MARK KRAMER, FDA Office of Combination Products

ASHLEY B. BOAM, MSBE, CDRH

RICHARD P. FELTEN, CDRH

DAN SHAMES, M.D., CDER

JESSE GOODMAN, M.D., FDA

NANCY ISAAC, Aerogen

C-O-N-T-E-N-T-S

P-R-O-C-E-E-D-I-N-G-S

(8:14 a.m..)

DR. PROVOST: Good morning. We're going to go ahead and get started.

My name is Mariam Provost. I work for the FDA and the Center for Devices and Radiological Health.

And I just want to make a few announcements before we introduce the first speaker. I also want to say welcome to the people across the hall on watching us on the TV and also people who are phoning in. We also are providing this conference through an audio hookup. So welcome to everybody.

And I also want to say thank you to all of the speakers who have agreed to come today. I think we have a very interesting program. It's a very full program. So there's just a couple of things that I want to mention.

In order so that we can stay on time as best we can, we have structured the morning session so that there's a question and answer period. So we

would ask that if you do have questions, if you could wait until the question and answer period to ask them, I think that will help us to keep on time.

I also do want to mention there is going to be a panel discussion at the end of the day. So if you don't get a chance to ask some burning questions because of the limited time, you can save your questions for the end of the day, and we do have 45 minutes set aside for panel discussion.

We are, as I mentioned, audio broadcasting this conference. It's also being transcribed. So if you do have a question, we ask that you identify yourself and also please speak into the microphone so that everybody can hear.

And, finally, very important, lunch. We're a pretty big group here today. So that everybody can get lunch and get lunch on time, we've arranged with the hotel to provide a box lunch, and there is an attendant from the hotel who is here out in the hallway, and they ask that you order the lunch by 9:30 this morning.

So if you want to get a lunch, please, I

urge you to order your lunch now so that it will be here when you need it.

And that's all for the announcements of that type. I would just like to introduce Dr. David Feigal, who is the Director of the Center for Devices and Radiological Health, who is going to give us some welcoming remarks.

(Applause.)

DR. FEIGAL: Well, thanks.

One of the most important things that I could do this morning is to thank Mariam Provost and Vickie Babb, who arranged this meeting on relatively short notice as far as meetings go, and the challenge of finding a room like this that's ideally configured for talks and speeches. The only one that actually was more interesting was one once where we had a lot of press with lights, and it had mirrored columns all around the room.

(Laughter.)

DR. FEIGAL: So every time they would turn it was like begin inside a prism. It was very interesting.

One of the real challenges in medical product development is to bring the first of a kind to the market. As we've looked back at what kinds of applications are approved rapidly and which applications take longer, it's quite clear that the first of a kind products are often difficult.

It's also very clear that if we can sit down and have a discussion of what is needed to establish the kinds of information that you need to bring a product to market, that you can facilitate this process. And there are times when this is done quite formally in the shape of developing guidances.

There are other times when it seems to evolve product by product.

Now, it's challenging to bring one new product to market. It's even more challenging when you have a combination of products. When you have two products, one of which may be novel, both of which may be novel, you have particular challenges to know exactly what is the regulatory path going to be.

It's also a challenge when you yoke

together a pharmaceutical, which often comes from a very large and well resourced company, with the device industry where many of the innovators are small companies work on closer margins, on more rapid cycles.

There's a difference in the way that the intellectual property of devices is protected than drugs. So there are many, many challenges, and as we looked for topics that we could address and begin to develop, the whole concept of combination products and particularly products where there was a novel mechanism of delivering a drug or a biological therapeutic seem to be particularly timely.

So my task this morning is to moderate the session, introduce our speakers, and this afternoon we'll come back and have time to actually more explicitly talk about some of the regulatory challenges.

As you are aware, if you followed some of the developments in the center in the last four or five years, we view the regulatory process as an intensely scientific one. This isn't a type of a

decision-making that can be done simply by developing checklists and looking for completeness or other types of processes.

So it's appropriate that we begin this morning with an intense look at some of the science and some of the exciting science in some of the important disease areas, and that we begin the morning with some remarks from Dr. Mark McClellan, who is Commissioner of the FDA and who is responsible for this meeting, which will probably just be the start of a series of workshop-styled meetings on product development.

So with that, let me turn the mic over to Mark and let's get started.

DR. McCLELLAN: Thank you, David.

It's a pleasure to be here with you all this morning at this new workshop on innovative systems for the delivery of drugs and biologics. This is a particularly important pleasure for me because of all of the people here with our devices center and with the biologics center and our drugs center who have contributed to this effort.

As David mentioned, this is an early effort in what I think will be a series of programs designed to focus on the important questions of emerging technologies and our effective approaches to regulating them, to demonstrating that they're safe and effective in getting better treatments to patients as quickly as possible.

I also want to spend a minute thanking Dr. Robert Langer for his work and his contribution to FDA, in general, and to this meeting, in particular. Dr. Langer just finished as Chair of our Science Board for several years, and that was only one of many efforts in improving biomedical technology.

Dr. Langer is a professor at MIT who has made many contributions in chemical and biological engineering, ranging from insights in basic science and improvements in biomedical technology to actually bringing those products to market through patents and through the development process.

And I think Dr. Langer's efforts exemplify the kind of work that we want to highlight

here and the kind of perspectives that we want to bring to the FDA's efforts in these development workshops.

One of his recent articles, which is in the packet included for this meeting, is on how to get drugs where they need to go, and I think this conference and the efforts that will follow from it are an effort to build on that by figuring out how to get drugs where they need to go quicker and more effectively and more safely. That's the goal that we are attempting to fill with this workshop effort.

As Dr. Feigal mentioned, this is the first in a number of workshop that have developed from a strategic planning process that we've undertaken at the FDA over the last six months or so. This is an effort to develop clear guidance, clear regulatory pathways for product developers in a range of innovative areas. It includes not only novel systems for delivering drugs and biologics where they need to go, but also such areas as pharmacogenomics and cell and gene therapy, as well as many priority areas for product development, such

as cancer treatments, obesity treatments, and treatments for diabetes.

In our strategic planning process, these were areas where our staff felt that there were opportunities if not to actually identify more clear and effective regulatory pathways, at least a need to take stock of recent developments in the sciences as applied to product development.

And so that's why we're having these activities where we can get people together and figure out if there are clear ways in which we could improve regulatory pathways. This is more important today than ever because of the tremendous potential out there for improvements in medical technology.

You all are quite familiar with what innovations in health care have brought to patients in recent decades. For example, treatment of heart attack, which used to involve largely supportive care as recently as a few decades ago, has transformed as a result of innovations in drugs, biologics, devices, and combination products, has transformed heart attack care into a condition that

most people now should expect to survive.

This is a big change in recent decades. Diabetes is also an area where tremendous changes have occurred, and some of the greatest improvements in the treatment of these conditions have come from combination products, devices and drugs, devices and biologics working together. These involve treatments that may permit the delivery of medications more accurately and effectively, as is the case in a product that we approved yesterday that combined a blood sugar monitoring system with a continuous insulin delivery pump to permit more accurate and at least the promise of more accurate and timely delivery of insulin on an ongoing basis.

It includes treatments that permit drugs to get to the right place in the body more accurately, as in some of the liposomal delivery systems that have been developed recently. It includes ways of targeting particular cells more effectively, for example, through new nanotechnologies.

So there are many applications of new

technology in the area of combination products, and the potential for these technologies to have an impact on improving patient care in the years ahead, I think, is even greater. But it's not something that's going to happen automatically.

And one of the things that has concerned me since coming to FDA is all that I've been able to learn about some of the challenges facing product development today. If you look at just plain, old drugs, small molecule drugs which in many ways are not the only kind of innovative treatment coming along now, the development process has gotten considerably longer and more expensive, and this is not something I think is the fault of regulation primarily or maybe even at all, but it is a fact.

It now costs, according to some estimates, over $800 million to develop a new drug, and while that number is somewhat controversial, there's no arguing with the fact that it has gotten a lot more expensive than it used to be because of a more extensive preclinical development and testing process.

It has also gotten more uncertain than it used to be with only a small fraction of the drugs that enter clinical development actually resulting in applications to the FDA and only less than one in two that make it even to the advanced phases of clinical testing, the so-called Phase III trials, resulting in applications to FDA.

And in the past few years, we've seen a downturn in the number of new product applications coming into the agency, and so that's an area of concern where, on the one hand, the amount of investment in new research and development both in the private sector and in the government through increases in the NIH budget have reached an all time high, but on the other hand, we're not yet seeing that translate into a significant upturn in the number of valuable new products reaching patients.

And this may be something that is just going to take a matter of time to resolve. I've got a lot of long term confidence in the biomedical industry to improve care, but this delay is something that adds to health care costs because of

the cost that goes along with developing new products and has an impact on quality of care because it results in longer times before patients can get access to safe and effective new treatments.

So this is a real challenge as products become more complex, and in meeting this challenge FDA can and will maintain its gold standard for the world for product approvals. That means we will continue to make sure that products are safe and effective before we approve them.

At the same time, with all of these insights coming in the form of new products, I think there are opportunities to find way to make that development process work more efficiently. Again, this is not something that the agency can solve by itself through just reducing review times and the like. It's something that will require some creative thinking and efforts to make sure we are applying the best and latest translational science to our regulatory processes, to make sure that we are using the most effective mechanisms for designing studies, for developing endpoints, for

doing follow-up studies after approval and the like, to get to our determinations of safety and effectiveness as efficiently as possible.

So as part of this effort, which is a key element in FDA's strategic plan, we announced a new FDA initiative on improving medical innovation earlier this year. The goal of this set of efforts is to bring more clarity and consistency to the review process for new and emerging medical technologies, and we're aiming to do that in several ways.

First, as Dr. Feigal mentioned, we're conducting an internal review, a root cause analysis of cases where new products took more than one cycle to reach a determination of safety and effectiveness.

In our preliminary results, it looks like in a lot of cases the multiple cycles were unavoidable. New things were discovered in development process late, clinical results that were unanticipated, that required some further evaluation and the like.

But in some cases, it appeared that earlier and clearer communication with product developers about the standards for approval and about what exactly was required for approval would have helped, would have helped them get it right the first time on their product applications.

So a couple of the other major components of this initiative are designed to try to address that issue.

We are also doing a number of guidance development programs like this meeting here today. This discussion is intended to lead to written guidance that can help in the development of products in the area of novel delivery systems for drugs and biologics, and I mentioned some other areas of emerging technology where we are conducting similar kinds of activities.

In addition, we are in the process of implementing some quality systems for product reviews. We have a lot of expertise in the agency on the best ways to approve and review new products, and we want to make sure that the best practices in

various parts of our agency are shared throughout the agency and are used to implement more efficient regulatory processes.

And this is something that we are undertaking, in part, in conjunction with outside consultants in developing better performance measures, in part through internal work to identify best practices, develop performance measures related to them, and implement them more widely throughout the agency.

So these are all major elements of our effort to improve the innovation process, but I wanted to ask you to take a step back and think more broadly about this. Most of the time and product development obviously doesn't occur in the review times at the FDA. Most of the time in product development occurs between the time someone has a good idea in the basic biomedical sciences of a proof of concept and then starts moving that idea into preclinical and then clinical testing.

That's a process that can take many years and, as I mentioned earlier, can be very

costly and have many uncertainties along the way. Anything that we can do through clarifying what our regulatory standards are to make that part of the process work more efficiently as well will only add to these potential savings and reductions in uncertainty in the process of product development.

So it's not just about our review time. It's about clarity in what is needed for determining that a product is safe and effective, and so that's why it's very important to have many of you here today who are involved in product development, who have terrific experience in the regulatory process and who can give us hopefully some insights that can serve as a basis for our written guidance to make this whole process work more efficiently in such emerging areas of technology as novel systems for delivering drugs and biologics.

This is an area where these combination product areas have not gone as smoothly as they might in the past, and we are already taking some steps to try to address that. One of the first things that I did as Commissioner was set up a new

Office of Combination Products, headed by the very capable Mark Kramer, in the Office of the Commissioner to provide better oversight and to help develop clear guidance about jurisdictional issues and other issues that are unique to combination products.

One of the other things that I'm working hard on now with Dr. Feigal and the rest of CDRH and our Office of Combination Products is the effective implementation of the new Medical Device User Fee and Modernization Act. This is a very important piece of legislation that will give us additional resources not only to turn around reviews more quickly, but hopefully to spend some more time and effort on identifying more efficient regulatory practices, to have those kinds of early conversations with product developers that help us by making sure we understand some of the latest technologies that are coming along and how to best evaluate them, and to help product developers by giving them some of our insights in terms of what it actually takes to demonstrate that a product is safe

and effective and meets FDA's regulatory standards.

We are fully committed to the goals of the Medical Device Users Fee Modernization Act, and we will implement this program successfully. We're working closely with OMB and others on Capitol Hill to make sure that the adequate funding will be there to meet those program goals, and we're going to succeed.

So this is a very important time in product development for combination products and novel drug and biologic delivery systems for a number of reasons. We've got new resources. We have new programs in place already, and we have a strong commitment from the people at CDRH, CBER, and CDER to find more effective ways to implement, to determine that these new technologies coming along are safe and effective, and it couldn't happen at a more critical time with the investment in biomedical R&D in these combination product areas at the highest levels ever and the potential for important new technologies reaching patients.

If we can demonstrate they're safe and

effective, the potential is greater than ever. So this is a critical time for health policy. We think that at FDA we're in a great position to help with this innovation process, and we've got more experience and data on the factors that influence success or failure of new treatments than anyone else, and we want to find ways to bring that knowledge to bear and bring some of the new insights in biomedical research to bear in these areas as effectively as possible.

So I am looking forward to hearing from all of you here today and hearing about the results of this conference. It sounds like a great set of sessions this morning on reviewing some promising clinical applications in the areas of novel delivery systems and some of the preclinical challenges, this afternoon moving on to perspectives from product developers and the FDA on challenges for product development, all with the goal of finding a clear basis for the regulatory processes that we require for demonstrating the products are safe and effective, and getting safe and effective products

to market as inexpensively and with as little uncertainty as possible.

Thank you all for participating in this effort. As I said, this is, I hope, going to be an early step in an ongoing effort to make sure that our regulatory processes are up to date and are helping patients get access to safe and effective treatments as quickly as possible and at the lowest possible cost.

And we definitely need this to be a collaborative effort. We've got a lot of good ideas internally. We need to bounce them off people outside the agency, and there are also a lot of good ideas outside, given all of the progress that has occurred recently in such areas as novel delivery systems.

So this seems like the right time and the right topic for a kickoff conference on improving innovation process, and I want to thank you all again for coming here today and also for listening to me this morning.

Thanks very much.

(Applause.)

DR. FEIGAL: Well, it's my pleasure this morning to introduce our keynote speaker, Professor Robert Langer. Again, thanks are in order for the service that he provided by chairing the Science Board, and part of that time period was when the center itself actually went through an external review of our science program. So we appreciated his efforts in that very much.

Dr. Langer is the Kenneth J. Germeshausen, Professor of Chemical and Biomedical Engineering at MIT and is a member of the National Academy of Engineering, National Academy of Sciences, and the Institute of Medicine, one of the few people to hold memberships in all three of those academies.

The kinds and nature of the contributions that Professor Langer have made are particularly relevant to our program here today, and without any further ado, let me ask Dr. Langer to come and begin.

(Applause.)

DR. LANGER: David and Mark, thank you very much. It's an honor for me to be able to speak to you all today, and it was certainly an honor for me to work with the FDA as well.

I've had the fortune over the years of giving a lot of talks. Usually I end up giving them at universities, though I've given them at companies, too. And usually what I talk about are drug delivery systems.

A few years ago, though, I was giving a talk at the University of California at Berkeley. So it was the other side of the country, and I got in very late at night, and I was trying to think how to introduce my talk. And I thought for a second and I said, "Well, probably everyone here has taken drugs."

(Laughter.)

DR. LANGER: That's what they did, too. They laughed, but of course, what I meant were drugs like all the ones that are regulated by FDA, and that is what I want to talk about today.

In particular, what I will try to do

this morning is to give you an overview, and obviously it can't be complete, but what I'll try to do is go over a little bit about why drug delivery is important, where it is in terms of some of the products, and where it's going.

Let me start with a slide. I just want to make sure. Do I do something to get this on? I'll try to tell some more jokes in the meantime.

(Pause in proceedings.)

DR. LANGER: So anyhow, I think I can do this almost without slides, but at least the first couple of ones.

Thank you very much, Mary.

So what I was going to say, and people obviously have probably seen things like this before, but if you take a drug, really any drug and really by almost any means, mouth, skin, whatever, the drug level starts out very low, reaches a peak, and then goes down, and that peak and valley level, the problem is those peaks can cause huge safety problems, sometimes death, and the valleys, the drugs, are not effective.

One example I sometimes use in class are, you know, sleeping pills. If you take too much you could die. If you take too little, you don't go to sleep. I mean, there's various ones you could think about.

So that provides the motivation for could you come up with a way -- and this is not always what you want to do, but for a lot of cases what you'd like to be able to do is take a drug and have it go to the desired range and stay there for as long as possible.

Let me just give you a striking example of that that ALZA did working with Pfizer. So they had a drug that was called Nifedipine, which also is known as Procardia, a calcium channel blocker, and all throughout the 1980s it was taken by a soft gelatin capsule, so sort of immediate release. It was quite a successful product. It sold about $300 million a year.

It was always, though, if you took it and got the soft gelatin capsule, peaks and valleys just like you saw.

ALZA, using an osmotic pump system, and I'll mention that a little bit more later, figured out a way to get it at pretty constant release. That product actually became very successful. Not only was it used for angina. It also got a new approval for congestive heart failure.

What happened if you looked at the side effects are huge. Here you can just look at the comparison of the two, and if you compare things like headaches or flushing or dizziness or palpitations, there's a huge difference.

Taking the controlled release form you get many, many fewer side effects than the soft gelatin capsule form, and from a cost standpoint, from the company's standpoint, it became a $1.5 billion a year product rather quickly.

Let me mention a few products to just give you an idea, though I imagine people are aware of this, of the range of things that are already being used in this actually very young field. I think if you look at this, almost all controlled release systems at least that I'll be talking about,

will be approved in the last 20 years or the last 21 years. This was about one of the earliest ones.

It's the nitroglycerine patch, one of a number of transdermal systems that can deliver drugs just passively in this case through the skin. Here it does it for a 24-hour period. Over 500 million of these were used last year.

This is the longest. Sometimes people ask me how long can a controlled drug delivery system go. Well, this is the longest one that I know of. This is the Norplant. These are little silicone capsules that you can place underneath the skin for contraception. They're approved in over 50 countries.

And what you can see here is these capsules, which are simply the size of match sticks, are able to release the drug for over 2,000 days or five years from these tiny little implants.

This is the very first controlled release system for a protein. For many years people didn't think you could ever deliver proteins. Alcames, which is a company I've been associated

with for a number of years, developed along with Genentec tiny little microcapsules that you could put human growth hormone in.

Normally a patient with pituitary dwarfism would take the shots once a day. Now with this you could take them once a month.

And another one, the last that I'll mention at least right now is really a very innovative thing that ALZA did for Ritalin. If any of you have children that have attention hyper deficit disorder, they may take this.

Normally what people had to do was take Ritalin, you know, several times a day, and if you're a small child that means you might have to go to the nurse. It might be embarrassing, and maybe it doesn't even work as well in the regular forms.

ALZA discovered that actually you don't only want to get steady release. You actually want to have a time where the release is increasing, and because they were able to design a special version of an osmotic pump shown here where they've got an overcoat, they're actually able to do this.

So they developed a system called Concerta based on an osmotic pill that you could take, a child could take generally once a day to treat ADHD.

Let me just give you some statistics, again, for part of this overview that adverse drug effects where people take drugs kind of the way they're supposed to, they can cause up to 15 percent of hospital admissions. This was in JAMA a few years ago. One hundred thousand deaths; that's more than four times the number of deaths caused by AIDS in this country, $136 billion in health care costs.

Patient compliance, that can cause up to ten percent of hospital admissions, particularly in the elderly that forget to take drugs.

And of course, one of the things that motivates a lot of companies, which it should, is can you make a profit in this area. And if you look at this, as I mentioned, controlled drug delivery systems in the 1980s, the sales were about zero. In 2001, they're about $20 billion, and my expectation is that number will go up rapidly for a single

reason that I'll mention later and will be talked about later today.

Just look at drug eluting stents, totally based on controlled release technology. Sales are projected to be five to seven billion dollars rather quickly. So there's enormous opportunity in this area, as well.

The advantages of controlled drug delivery are reduction of adverse side effects, which I've mentioned. You can keep drug levels in the desirable range, and much less drug is desired.

You get improved patient compliance, and as we will go over all day, new therapies are possible.

People -- I just want to grab myself some water -- people, you know, you can approach drug delivery from a number of standpoints. One standpoint is pretty much every part of the body -- this may be a little hard to see in the back -- but I think that sometimes people ask me, "Will there ever be an ideal delivery system that you could just take by one way?" And I think the answer is no.

People have been successful at delivering drugs orally, nasally, transdermally, through the lung, transmucosally, like vaginal, buccal, in the eye, by liposomes, by injection. All of these, almost all of them are multi-billion dollar markets in and of themselves.

So there have been successful products in almost all of these areas, and I expect that that will continue because there's enormous opportunity in each of these areas. There's specific diseases in some of those areas, and many of these areas can be a portal to the rest of the body for delivering drugs.

I thought I would try to focus in the interest of some of the goals of this meeting on four areas: the need for new materials; nanotechnologies; noninvasive delivery; and high throughput approaches.

So I'll focus on each of these just in context to illustrate what I see as some of the ongoing work and some of the challenges ahead.

First, let me go over new materials.

You know, this is something that I got involved in personally in the 1970s. I was actually very surprised to see this. My own background is a chemical engineer, but when I got done with my degree I worked at Boston Children's Hospital, and being a chemical engineer, I guess I just thought naively that the people who were driving the work for bringing new materials into medicine would have been older chemical engineers or chemists or material scientists.

But when I looked into this, I found that it was rarely the case. Almost always the driving force for bringing materials into medicine were clinicians, and they wanted to solve a problem and solve it as quickly as they could, which is good.

But what they would do is generally they would take a material that was usually in their house and that kind of resembled the organ or tissue they wanted to fix, and they'd use it in the human body. And that led to some progress, but also to some problems.

And just to give you some examples, this may be cut off a little bit, but it's an artificial heart. But you probably figured that out. Anyhow, let me just tell you a story or two, and these are all true.

In 1967, clinicians at the NIH wanted to come with an artificial heart, and they wanted something with a good flex life, you know, for a heart. And they said, "What object has a good flex life?"

And they said a lady's girdle material. What's that made out of? It's made out of polyetherurethane. So that's what they began to make the artificial heart out of. That was 1967.

Now we're in 2003. It's still made of that, and you can imagine from a regulatory standpoint once you start going down that path it's not so easy to stop. And that happens in many different areas. Dialysis tubing was originally sausage casing. Vascular graft, that's an artificial blood vessel. It was a surgeon in Texas going to clothes store, and breast implants. One of

those was a lubricant -- oh, thank you -- one was a lubricant. The other was a mattress stuffing. Probably you figured out the logic.

But these are all true, and that's often how materials have come into medicine, and I started thinking in the '70s, well, you know, maybe you could take a different approach, and I believe we're going to start to see more and more of that today.

And that is rather than take these materials that might exist in your house, could you actually ask the question what do you really want in a biomedical material or drug delivery system from a chemistry standpoint, biology standpoint and engineering standpoint, and could you synthesize it from first principles.

I thought I'd give you an example.

At any rate, let me give you that example. When we started in the 1970s, there was only one material approved by the FDA that was synthetic degradable material, suture materials like polyesters, and they displayed bulk erosion kind of like this. So it would start out -- now this isn't

working either. That's okay. I'll go over here. I'll get some exercise this morning. Oh, but I think -- is that going to be a problem?

(Laughter.)

DR. LANGER: Maybe we had better get one that works. Anyhow, so it might be good if we got one that works. At any rate, I'll try to do this with my pointing. It might be harder on some of the slides.

Thank you very, very much. Will you remind me to give it back up? Okay. I got it. Thank you very much.

Okay. So bulk erosion, usually you put the drug uniformly throughout. It starts out getting spongy, and then it could fall apart. That, by the way, is fine for a lot of drugs, but if you had a really toxic drug like, say, insulin or a cancer drug, it might not be so good because you could get bursts of the drug coming out.

So we said from an engineering standpoint what you'd really like is this: surface erosion, kind of like the way a bar of soap

dissolves. So the challenge is how could you do it.

So I won't go through all of the chemistry, but basically what we did is we took this from an engineering design standpoint. We said, well, what are the right bonds. We thought anhydride bonds. We thought what are the right monomers, and we came up with a couple of monomers, very hydrophobic ones that could keep water out. This is extremely hydrophobic CPPP, and sebacic acid is a little less so.

What was interesting is that by simply adjusting the ratio of those two not only could you get surface erosion, but you could get these to dissolve at almost any rate you want, from zero percent sebacic acid. So about eight percent is gone in 14 weeks. It will take three or four years for one of these to dissolve fully.

But if you add a little bit more sebacic acid, it dissolves faster- that's 15 percent, 55 percent, it dissolves faster, 79 percent it's all gone in two weeks.

So you could simply dial in your monomer

ratio and make these last for whatever length of time you want.

So with that, you could think about using it for all kinds of applications. One of the early applications that came up was Henry Brown, a young neurosurgeon -- he's now head of neurosurgery, chief of neurosurgery at Johns Hopkins -- came to see me in the 1980s, mid-1980s, and he said, "Could we change the way people do chemotherapy with this kind of approach? Could we do local chemotherapy?"

So here was the idea. He would normally go in, operate on patients, take as much of the tumor out as he could in the brain. He would always do this, as would everybody else. But he said is after that, you know, they have to give this drug, BCNU, intravenously. Could we do local chemotherapy? This drug is enormously toxic.

So the idea was could you take polymers like this, allow him as a neurosurgeon to put the drug in in little wafers that would locally deliver it to any remaining tumor he couldn't get. The idea is that could tremendously spare the body the side

effects of this terribly toxic drug, but give high concentrations right to the brain tumor where you want it to be.

So let me just show you that. If anybody is squeamish and doesn't like to look at blood -- and I'm serious about this -- don't look, but here is what it looks like, a little wafer the size of a dime going in. Usually you put seven or eight and then close it up.

I always show those slides rather quickly. You know, it's very hard to get good advice when you give a talk, but a few years ago my wife Laura came to one of my talks. She's a neuroscientist, and I asked her at the end. I actually was showing those slides.

I said, "What did you think of the talk?"

And she said, "Well, Bob, the talk was okay." That's actually very high praise.

(Laughter.)

DR. LANGER: But she said, "You know, there was this 12-minute period of that talk where

you had those two bloody slides on and you explained every detail of it to the audience." This was all chemical engineers I was speaking to, and she said, "I don't know if you were looking, but they were all turning green and looking at the floor."

So ever after that I've done just what I did today, showed them real quickly and I warn people. But I do want to tell you a sequel to that. I give talks to lots of different groups, and I happened to be giving a dinner speech to a group of neurosurgeons and neurologists, all M.D.s, and I did the same thing, and at the end of the talk a number of the neurosurgeons came up to me and they said, "You know those two bloody slides you showed?"

I said, "Yes."

They said, "Those were fine. No problem," but they said, "Those chemical formulas."

(Laughter.)

DR. LANGER: You know, right after dinner. So you have to be very careful who you speak to.

(Laughter.)

DR. LANGER: At any rate, there are a lot of challenges -- I'm just going to go back a slide -- that we had to overcome, which are typical I think in any of these areas, and I'll just go over those briefly. These were all actually things at the National Institutes of Health Study Sections, other professors told us why we couldn't get it to work, but basically it's just a synthesis, reactivity, strength of the material, toxicity, diffusion of the drug, manufacturing, and so forth.

All of these were challenges that had to be overcome. Actually they made for a lot of good theses in our lab. Later on we licensed to do a company, Guilford Pharmaceutical, and actually the FDA did approve this originally in 1996. It was the first time that a local chemotherapy system got approved. That was approved in 1996 for recurrent glioblastoma. It was extended this year for primary glioblastoma, but it's an example which I wanted to pick of how you could use new materials to create new therapies in drug delivery.

Also, it illustrates a very early

example of local chemotherapy, which I think is very powerful, and of course, I think the most powerful example of that which you'll hear more about later today is applying this idea to coated stents where basically you put stents in to keep blood vessels open, but the problem is, as people will hear about, that for a fairly high percentage of the time those vessels will close due to restenosis, smooth muscle proliferation, and so forth.

But you can take some pretty toxic drugs like Taxol and repromicin or others, put them on a tiny polymer film, locally deliver them, and the results have been very, very dramatic by many companies in terms of keeping these blood vessels open.

That's the first topic that I wanted to mention, is this idea then of new materials and local delivery.

The second is nanotechnology. Nanotechnology is something I'm sure everybody reads about in the newspapers. Probably everybody wonders what it really is. Even I wonder what it is

sometimes because it has so many definitions.

But I think there's several ways nanotechnology can make a huge impact, and I thought I'd give you a couple of examples.

The first actually is work that was done originally by John Santini when he was my graduate student at MIT and now president of MicroCHIPS, which is a company I'm also affiliated with. I had this idea about ten years ago. I was watching this TV show on how microchips are made in the computer industry, like Intel, and I thought, gee, this would be a very interesting way of doing drug delivery.

So along with Michael Sema and John, we came up with originally a very early design, which I'm showing here, and the idea is rather than take a chip for your television set or your computer, what you could do is build little nanowells -- I'll show you these in a minute -- into little chips. Originally they were made of silicon and covered with gold.

They can, by the way -- some of our more recent students have made them out of polymers.

They can be made out of almost anything, but basically you can build little wells into them. This is a cut-away. So on one side there's an impermeable epoxy, and here we're using gold as sort of the cover. They're hermetically sealed. You can actually keep them on the shelf or in the body for a couple of years. Nothing will happen.

But if you apply selectively one volt to any of these welds, they're all individually addressable. What will happen is the gold will come off, and the drug will come right out. And you can program these to get almost any delivery pattern you want because if you want to get instantaneous release, well, then you just have the gold come off.

But let's say you wanted the release to be more slow. You could put a polymer or a gel right underneath it. Also, you could deliver one drug multiple times. I'll show you an example of that in a Pulsatile fashion, but if you wanted to actually delivery many drugs, like say we've often considered this like a pharmacy on a chip, you could do that. If the drugs are potent enough, you could

put all of the drugs you want on such a chip.

And you can make them very tiny like nano, which is what I'm talking about, but you could make them bigger, too, if you had drugs that were less potent.

Let me actually show you what they look like in a picture. This is from MicroCHIPS, and this is a real good example of nanotechnology. These are pencils, and here's the chip. Here's one side and here's the other. There's hundreds of wells. Each of these contains a different drug or the same drug at a different dose.

And then what's done to use these, they're battery powered, and you could control them by telemetry. In other words, the same way you might open up a garage door, you could open any of these wells. You could envision a day when you might have a wristwatch or some unit like that that you could just do remote control, and you could open up any individual well whenever you want. And then it's like encased in something like a little pacemaker.

Also what I believe we'll see in the further future is even very smart systems where you could put biocensors -- I think Dr. Klonoff may talk about this more -- where you could put biocensors on these chips along with a microprocessor and a power source, and you could get direct control.

Let me actually show you how this works. What I'm going to show you is a quick video. You have to look quickly, but I'm going to just show you a single well where you're going to be looking at the top of the well, and then we're just going to apply this one volt selectively, and what you're going to see is the top dissolve, and then you'll see a little conical bottom, and so let's take a look at that.

Here's the video. This is the top. Immediately the gold came right off. As soon as it does, the drug can come out. So basically it's just that quick. It can be made instantaneous.

Here's an in vivo. This is done in animals, and this just shows you you can get very reproducible Pulsatile release of the single drug,

and you could do this with multiple drugs if you wanted to.

So this is, I think, one example of nanotechnology where you have little nanowells, and also a good example of another thing that people sometimes hear, MEMS devices, micro electrical mechanical system.

The second example of nanotechnology that I wanted to do is at a more molecular level. There are a whole range of different polymer therapeutics that you might think about as nanosized medicines. Some of these are things like polymer drugs. You could actually take a drug, and I'll give you examples in a minute, but I just wanted to show you the range and also the sizes so that you could have polymers combined to drugs which could change the drug's properties.

You can have polymer protein conjugates A very good example of this which we hear a lot about are PEGylated, and I'll mention this more. You could take a protein, which might normally have a short half life or might be immunogenic, and yet

you can conjugate polyethylene glycol to it, and change both of those.

Another example are polymers for DNA delivery, and I'll talk about this more, but it's a huge area because if you wanted to deliver DNA, right now the only way to do it is with viral vectors, and I think everybody here at the FDA and elsewhere have made it pretty clear there are some huge safety issues with it.

Could you make nanosized polymers -- and I'll mention a method later -- where you might be able to make a polymer behave like a virus, but without the safety problems associated with it?

Polymer drug conjugates where you could actually target the drug to a particular place in the body, like, say, a tumor.

And finally, micelles.

So all of these things are being studied. I'll just go over one or two a little bit, but some of them are already approved. The first one is the drug attached to a polymer that's been approved for liver cancer in Japan, and then there

are a variety of pegylated molecules like asparaginase, interferon on CGSF, which have been approved by the FDA for different diseases.

Now, these have made a very substantial impact on medicine already, but there's more coming, and some of the things that are coming are to really engineer drugs with polymers to get very desired properties. So maybe you could put in a targeting residue so that it would target to a receptor. Maybe you would have a biodegradable linker, and people are already studying these for cancer.

Apart of the basis for treating cancer is that a tumor has very leaky blood vessels. So you might imagine a polymer, since it's big. Well, if the blood vessel is not leaky, it's not going to get out.

But when it gets in the leaky region of the polymer, it will get out, and that's called the EPR effect. And there are a variety of these systems in various stages of clinical trials for delivering drugs like Taxol or camptothecin, and some of them even have targeting moieties on them,

like lactosamine.

So many, many that probably will keep the FDA busy over the next number of years.

The third thing that I wanted to go over is the idea of noninvasive delivery of complex molecules. Can you do it orally? This would be like a protein or DNA.

Can you do it transdermally? And I'll talk a little bit about both of these.

Pulmonary, actually somebody from Nektar is going to be speaking. So I thought I'd let them do that, and there's also various other routes that we might consider, but I'm going to just focus a little bit on these two today where there has been probably a lot of work done, as has there been there.

So first, oral. There has been at least four strategies that have been used: carriers, and I'll give an example of those; nanoparticles that might be able to be taken up by M cells, for example in the Pyrus patch (phonetic); targeting to various receptors in the gut or Pyrus patches.

And even bioadhesive approaches are being worked on by a variety of groups. I was just going to mention one briefly, which is the carrier approach, which is probably furthest along, and David Klonoff may talk about this more, too, but there's a company, Emispheres, which has synthesized some molecules which they call eligens, and their idea is to complex them to drugs, to deliver them transcellularly without compromising cell integrity.

And you see an example of this top panel here where insulin is being delivered to a cell monolayer at different concentrations, and you see it getting through, and yet the lower panel seems to show that it doesn't affect the tight junctions and so forth.

They've used this to deliver insulin in patients. This is oral insulin, and they have also used it to deliver human growth hormone.

Probably the big issue that will come up here for oral delivery with any of these things are two or three things. One is bioavailability. Do you get enough in? And two is safety, or do other

things also get transported? And these will be some of the key issues to look at.

Nonetheless, I think it's very exciting that we're already seeing a delivery of large molecules in people.

The second area that I want to talk about is the skin, and the skin has been a normally incredibly impenetrable barrier though right now there are ten transdermal products on the market, all by passive delivery, a $3 billion market, and some of them are huge, like Fentanyl patches, which are for pain management. People, I'm sure, are familiar with smoking cessation, and so forth.

Well, why is it so hard to get drugs through the skin? Well, first, I think we should all be very glad that it's hard because otherwise we'd get infected.

But what makes it hard is all of the resistance to the skin is the outermost part of it, the stratum corneum. It's only 15 cells layers thick, and it looks like a brick wall if you looked at it under the microscope. You have deal cells,

keratinocytes, and lipid bilayers here. So it's like bricks and mortar, and it provides a terrifically tight barrier to get through.

That being said, a variety of groups are trying to do this. Vyteris is a company, a spinoff of Becton-Dickinson, and they've developed an approach using iontophoresis. This is using an electric field basically to transport drugs across the skin. This is their system, and they've actually developed pretty advanced approaches. They are actually delivering in this case calcitonin in people this way.

ALZA, which has certainly been a leader in transdermal drug delivery, has developed what we call the E-TRANS system, and here they're putting Fentanyl, the drug I mentioned, which they've worked on with Johnson & Johnson, which has been very, very successful, and here they're putting it on the skin, and it slowly delivers it, but as I'll show you, by applying the electric field, and this is sort of what it looks like; they've got an on demand button, a red light diode. This is kind of the structure of

it.

But what you can do is if you want to get a pulse of Fentanyl, feel more pain, you can just do this rather quickly. So this can actually provide Pulsatile Fentanyl delivery using, again, iontophoresis.

And here we're looking at them delivering another peptide. This is luteinizing hormone releasing hormone in a Pulsatile fashion. This is a drug that people might use for fertility control. It has also been used for other treatments as well.

ALZA has also developed a kind of micro needle approach. As I mentioned, really if you want to deliver a drug through the skin, if you could get through relatively painlessly that thin stratum corneum, you could deliver a drug. So they've developed what's called the macroflux transdermal patch, which has these little protrusions. You can put it in the skin, and here they've done like an example of delivering what are called anti-sensal nucleotides (phonetic). These are about 7,000

molecular weight through the skin this way. So that's another approach.

And the final transdermal approach that I wanted to mention is one that I've been involved in. You'll see Coats in our laboratory and then Santra Company that we've been involved in that has developed what's called the SonoPrep system, and the idea is you can take ultrasound, and this probably gets an order of magnitude more increase in flux than you get with iontophoresis, but it's at an earlier stage.

But the idea is that you can apply the ultrasound maybe for about 15 seconds, and that will permeabilize the skin. You could then put a patch on, and that patch, for example, could deliver insulin. Here's an example. You could actually lower blood sugar. It's being tested on man. You could deliver pain medications, and also I think what's particularly exciting is you could do noninvasive extraction.

Both Signas, a company in California, and Santra have been developing noninvasive ways.

Say if you open up the barrier for delivery, you could also open it up for getting interstitial fluid out, and so you might be able to, for example, which is in clinical trials now, detect glucose or many, many other different substances.

And again, I think we will see all examples of this someday

So the final thing that I wanted to go over today before summarizing is could we look at high throughput approaches, and I thought I'd give you two examples of that.

First, what I mean by high throughput approaches. If I looked at the pharmaceutical industry and I don't mean to be insulting by this, but from the formulation standpoint, it's sometimes a little bit slow. I mean, basically people make the drug, and then you have a formulation pharmaceutical R&D department, and they have to formulate it.

It's a huge, huge challenge as everybody knows, and I thought I'd just pick a couple of examples where you could maybe use high throughput

approaches to make these faster. One of them is gene therapy. As I've already mentioned, gene therapy is an area which I think is badly in need of better delivery systems.

In fact, it's interesting. If you talk to the gene therapy experts, like Endar Verma (phonetic), for example, I remember he was quoted a few years ago. Somebody asked him what are the three biggest problems in gene therapy. In other words, why is gene therapy not being used in patients today.

And he said, "Well, there are three big problems," he said, "delivery, delivery, and delivery."

And that I think is true. It has been a huge, huge problem, and it is unsolved. Richard Mulligan, whom I work closely with, another gene therapy expert, the same thing. How could se solve that?

Well, one strategy might be to come up with better viral vectors that would be safer. That's a strategy. Another might be nonviral

vectors. Could you make polymers that could behave like a virus, but without the safety problems of a virus?

And I won't go through that much of the science. I just want to illustrate the high throughput idea, but David Lynn, one of the graduate students in my lab -- he's now a professor at Wisconsin -- came up with the idea of synthesizing certain polymers that would, in fact, have many properties of like a virus. They would be taken up by cells and so forth.

But what was particularly interesting is he came up with a synthesis approach where he could make what are called polybeta amino esters, where he would simply take amines like this and conjugate them to diacrolates (phonetic) like this, and the idea is that with this particular set of chemical structures, he could take a whole range of commercially available starting materials. He could polymerize them in a single step. Many polymerizations, by the way, are done in many, many steps, but the particular beauty of this is there's

no byproduct. So no purification and no protection and de-production steps.

So you could actually set this up for high throughput. So Dan Anderson, another postdoc of mine -- this slide is a little busy, but it will get across the point -- basically what he did is he took 909 amino monomers. Those are shown here. Twenty-five diacrolate (phonetic) monomers, and he used a robot and developed high throughput synthesis methods and then also high throughput screening methods using cells, and what he was able to do in really a couple of weeks is make over 2,000 structurally diverse polymers, like a whole polymer library.

And here's the robot, and he could take these polymers, semi-automate it, cell based, and screen up all of these polymers, 1,000 in a day, and he found 46 new polymers. This is just coming out in publication very soon. Forty-six new polymers that could at least themselves deliver DNA as good or better as polyethylene amine, which is one of the standard polymer vectors.

Again, it's just an illustration, I mean, of where high throughput could make an impact, but I think there will be many other examples as people think about this.

And the final example that I wanted to pick is a company that I've been associated with called Transform Pharmaceuticals, and here the idea is could you apply high throughput approaches and robotics and bioinformatics to pharmaceutical formulations.

And Colin Gardner, who used to be VP of R&D at Merck, Sharpe & Dome, and now is chief scientific officer at Transform, has done this, but basically if you look at what we'll call form, which might be crystal structure, which is a real big deal in drug delivery and formulation. Traditionally, you might take a month or two and there's almost no informatics or data mining done. This is classical.

What Transform has done, and they're working with Johnson & Johnson, Eli Lilly, many other pharmaceutical companies, but basically they're able to because of the use of robotics

approaches, and I'll show you this in a minute or two, are able to do 200 to 20,000 experiments in two to four weeks, and every time they do an experiment, they use all of this informatics to tell them how to do the next set of experiments. So you can be faster and faster and smarter and smarter, and I think this is going to be the kind of way that will make sense more and more.

And let me illustrate that a little bit, and what I'll also do is show you a video to just give you a little feel for the high throughput idea that they're doing.

And in particular, what I want to show you is how they're analyzed. In other words, they're using robotics to make these things, but you also have to do analysis. Let's say you want to make a new crystal structure. How do you know that it's a new crystal structure or an old crystal structure?

So what they've done is they've used Raman Microscopy to analyze these, and I just thought I'd show you this video rather quickly.

So the idea -- if I can do this -- so here you're looking at the robot. It just takes the vial after all of these thousands and thousands of things, puts it into -- it's all done robotically, no people -- puts it in here, puts it under the microscope. Here's the crystal.

Now this is real time, looking at Raman spectrographs. Then it takes all of the data like this, mines them, and you see three crystal structures. So all done real time, and this, I expect, is going to be more and more what you could see in the future.

Well, does it make a difference? Let me just show you a couple of key publications that Transform has just done. They took acetaminophen. I think people are familiar with that. That's Tylenol, and they, by using this approach because you could do it so much faster, so much better, came out with the new crystal structure for Tylenol.

They did 10,000 experiments in three iterations in six weeks, published in JACS last year. So that's one example.

An even more striking example is this one, which certainly the FDA probably would be familiar with, Ritonavir. This was an Abbott drug. Here's what happened in initially. Abbott launched this drug for AIDS. It was originally in crystal form I, but 1.5 years after the launch, it converted it into an unanticipated crystal form. Sometimes this happens. Form II, but that form was 50 percent less soluble.

So Abbott obviously was compelled to recall and reformulate it. It cost them hundreds of millions of dollars and so forth.

Using the high throughput approach, what did Transform do in just a few weeks? Well, even though Abbott could never get Form I back, Transform, since they were able to do tens of thousands of these, got Form I back, got Form II obviously, also found three new forms that were never found before. So characterized them, you know, and made them.

This was just published in PNAS just a couple of months ago. Again, an illustration of

what high throughput might be able to do for you.

So let me end the talk by telling you some even further future challenges about what I expect, and I've been trying to keep on time. So I think some of the challenges which I've begun to touch on, they'll increase. One of the tremendously exciting things in the times we live in are all of the new pharmaceuticals that are being made.

Certainly we've had protein therapeutics for years, and yet there are still very serious delivery challenges. Today there's still only, you know, a few examples of the pegylated one and the neutropin depo where you can deliver proteins, and I think that the opportunity for delivering proteins is just huge, whether you could do it by controlled release to make it last longer or noninvasively. That will be very big.

DNA, obviously we've talked about that. Delivery is probably the central problem, and so there needs to be a lot of -- that's a big challenge.

And there's even newer things that are

coming out. People may be familiar with RNA interference. These are really incredibly exciting molecules. Our Science magazine called them the molecule of the year last year. These are very powerful, very specific units, about 20 base pairs of RNA that can interfere with cell function.

Another big area, and this was mentioned actually in Mark McClellan's introduction, is the delivery of cells. Could you deliver cells to the human body to create new tissues, a field we call tissue engineering?

And finally, I think there is going to be deliveries to new locales. In particular, one of the big areas I expect will be delivery to the back of the eye, just picking this as an example, which is clearly going to be critical because right now there are many new drugs that people are developing for treating diseases like macular degeneration or diabetic retinopathy, but the target is the retina, and these drugs, it's going to be very hard to get the drugs back there.

So there's a number of companies

developing approaches to deliver the drug to the back of the eye.

I think there's also enormous opportunities in other areas of the body, like could you deliver a drug to the nerves, for example to great herpes or other diseases, and I'm just really giving you -- and probably many, many others, delivery to the ears,. i.e., you know, for children. You could go on and on, but I think there's many great opportunities and yet many challenges where drug delivery can make a huge difference.

That's largely what I'd like to say to you today, but what I want to end with is one of the things that has been a personal pleasure for me is to be having been involved in the drug delivery field for now about 30 years. It has been wonderful to see the enormous progress that has been made by so many scientists and so many people throughout the world to the point where we see all of these kinds of therapies and many more that you'll hear about today that are really relieving suffering and prolonging life and obviously will do so more and

more in the years to come.

Thank you so very much.

(Applause.)

DR. FEIGAL: You did get us almost back on schedule, and we have time for some questions.

DR. LANGER: Maybe it was very clear and people want to leave very much.

DR. FEIGAL: Yes.

PARTICIPANT: (Inaudible.)

DR. LANGER: So the question is what are my thoughts on personalized medicine and individual therapy. Well, I think that that will come to pass. I think that in the genomic era we will see examples, you know, where we're learning more and more about individual people.

I think something like that microchip that I mentioned is a very interesting example of where you could some day, you know, create like this pharmacy in a chip for individuals. You know, maybe that would be a pill or a patch in some form, but I think that that drug delivery can make a huge impact in that area at some point.

Yes.

PARTICIPANT: (Inaudible.)

DR. LANGER: Would I like to speculate in the regulatory process? Actually, you know, let me make two points on that. The answer is no, but one thing I should --

(Laughter.)

DR. LANGER: -- but one thing I probably should have mentioned that I think also could be interesting by these techniques is actually record keeping. You know, I also think that when you do things by these kinds of smart medical things that, let's say, it was a chip or something else, that whenever somebody takes a medicine that you could actually get a permanent record of whatever drug somebody gets and, you know, have that transported to your computer so that that would probably be useful information for the FDA as well as the patients and doctors and medical companies to have.

It's hard to say. You know, when we deal with things like personalized medicine, it's, at this point, easy to say things will happen. I

think you have to break it down into individual cases to say exactly what the regulatory process would look like or should look like. I think it's too diffuse at this point really for me or probably anybody to comment on, other than to know that many years from now we'll probably see something like that.

DR. FEIGAL: Well, let me thank you very much for coming and joining us this morning.

DR. LANGER: It's a pleasure to see you.

DR. FEIGAL: Thank you.

DR. LANGER: Thank you.

(Applause.)

DR. FEIGAL: Well, continuing with our program and actually even with the novelty of being a little bit ahead of schedule, our next speaker this morning is David Klonoff, who is here from the Mills Peninsula Diabetes Research Institute in San Francisco, talking about how these technologies will have an impact on diabetes.

DR. KLONOFF: Good morning. I'd like to thank Dr. Provost and the people at the FDA for

inviting me to come out from California to talk about diabetes.

I'm an endocrinologist. My topic today is novel technologies for treatment of diabetes. I'll be discussing metabolic monitoring, the artificial pancreas, and alternate routes for administering insulin.

This is where I'm from, and this is the hospital that I work at in San Mateo, California. I'm editor of Diabetes Technology and Therapeutics, which is a journal that covers an area I'm very passionate about, which is new technology to help people with diabetes, and through the journal we also organize an annual diabetes technology meeting, and some of you in the room have attended that meeting.

When I was asked to discuss new technologies for delivery of insulin, I thought first that I would approach it from the standpoint of asking three questions. First, with respect to insulin, why develop this type of new technology?

What is the new technology?

And how good is the new technology?

So the first question I'm going to address is why develop the new technology. I think everybody knows that giving insulin through shots hurts. It's even in the latest issue of Popular Mechanics. Certainly all of my patients know insulin hurts, and basically that means that there are barriers to the use of insulin.

When I tell patients that they need to use insulin, they usually don't want to go onto insulin, and I think that if we can discover some new routes of insulin delivery, we can help overcome barriers to the use of insulin for patients who really need this drug.

And some of these barriers now include the pain and trauma from being pricked by an insulin injection needle, the inconvenience of carrying needles, and also the risk of hypoglycemia from an inadvertent excessive dose of insulin or hypoglycemia from rapid absorption of insulin.

So there's clearly room for new routes of insulin delivery. So the second question is:

what is the new technology? How can insulin be delivered?

Well, I'm going to be covering metabolic monitoring, as well as the other topics. So first, metabolic monitoring.

This is the current status of metabolic monitoring in diabetes. First, in terms of performance, the blood glucose monitors that are now available require less blood than ever, less times than ever to get the reading, and they provide more data management, better performance.

Second, they're greater options in terms of body fluids that are tested. It's not just blood anymore. In terms of sites, it's not just the fingertip anymore. And in terms of how automatic the readings are, it's not just whenever the patient remembers to check themself anymore.

Finally, we're starting to see a trend in integration. There are two themes in diabetes technology now. One is better blood glucose monitoring. One is better insulin delivery. They're starting to come together within products,

within the same product.

And so what we see is that these blood glucose monitors are now being linked to insulin delivery systems. So, again, the current status of metabolic monitoring is greater performance, greater options, greater integration.

I'm going to discuss the performance. The current level of performance of blood glucose monitors is that the blood volume that's required is now as little as 0.3 microliters, which is about one tenth of the volume that was required ten years ago. So we've come an order of magnitude in ten years.

Second, the measurement time. We can now get a reading in as little as five seconds, which is also one tenth of the time that was required ten years ago. This is quite a dramatic improvement in just ten years.

Finally, a typical blood glucose monitor can store up to 3,000 results. This goes along with the issue Dr. Langer raised about storing data, and this means that you can provide with this information mean blood glucose levels over the

previous one week, two weeks or four weeks, and this type of data can now be downloaded into a computer or to personal digital assistant.

That's performance. Next, as far as metabolic monitoring is the options. What we're seeing now is that we have options that are available on current blood glucose monitors, but we're seeing some new options that are emerging that are starting to become available and will become available in future blood glucose monitoring. These involve the body fluid sampled, the sites that are sampled, and what I call the automaticity, how often and how it's tested.

So where currently you've all seen a blood glucose monitor, it's invasive. It's jabbing the fingertip to get a sample of blood, and that hurts also. People don't like that.

What we'd like to see is more noninvasive or minimally invasive technology, and it's coming. It doesn't have to be the fingertip where all of the nerve endings are. People can now check blood glucose at alternate sites, such as the

forearm or the thigh. Fewer nerve endings; patients are more likely to want to test themselves.

Finally, the glucose testing is not just intermittent, but it can be done continuously, which means it does not require patient effort to remember to check themselves. So I'm going to cover each of these options.

First, the non -- minimally invasive, then the alternate site, and then the continuous. So regarding noninvasive and minimally invasive monitoring, first, I'm going to define noninvasive blood glucose monitoring. This is an area that all of my patients ask about: when is it going to be here?

A noninvasive blood glucose monitor generates and processes optical signals. It does not harvest body fluids, and it measures three compartments when optical energy is put into the body. It measures blood, interstitial fluid, and skin cells as a blended reading, and most of the noninvasive monitors that are being developed are using optical energy applied to the skin. There are

a few that are applied to the eye and instead could measure aqueous humor.

So what you see is you're applying an energy source, and it goes to these three body compartments, the blood, the interstitial fluid, and the intercellular fluid. They all reflect in some way, depending on the property of optical energy that's being used, the radiation into a detector, and you get a blended reading. And it's up to the engineers to sort this out and figure out how much glucose is in each compartment and whether there's any type of a lag between the reading that comes back out of interstitial fluid or intercellular fluid relative to blood.

Now, when you apply optical energy, there are various measurable effects of this light that can be measured, and it turns out that there's a scientist or company somewhere that's using every one of these principles of light to measure glucose, and part of the issue is finding the right wave length and the right type of energy.

But I've made a list of the measurable

effects on light that glucose can have. You can measure absorption of light or scattering, refraction, Raman scattering, rotation, fluorescence, impedance, photoacoustic heating, and there is at least one company working in each of these areas.

This is a picture from my hospital of a patient who has given permission to show his picture, having a noninvasive blood glucose test done. This is a glucose clamp study where we keep the blood sugar constant by infusing high doses of glucose and high doses of insulin, and then we can keep the glucose level constant for a long period and make multiple measurements. His right arm has three IVs in it. His left arm is on the noninvasive monitor which is purposely not being shown in this picture, but he's going to be here 12 hours for this study.

Now I'm going to discuss minimally invasive blood glucose monitoring. A minimal invasive blood glucose monitor means that the skin barrier is disrupted, but not a blood vessel. So

you're digging, but not all the way into a blood vessel. So what you're measuring is either interstitial fluid or some other extravascular fluid that's harvested from skin.

It turns out you can measure some type of a diluted interstitial fluid or real interstitial fluid. You can make a reading either intermittently, if you sort of drill intermittently, or you can leave the sensor under the skin, and then you can read a continuous reading. You can either pull the interstitial fluid out so that it will harvest it, so to speak, and measure it after it is out of the body, measure continuously, or you can leave a sensor under the skin and measure it continuously in the body.

There are a number of ways of pulling interstitial fluid out of the body, different types of ways of disrupting the skin so that you can measure the glucose concentration of the interstitial fluid, and it turns out in most cases that the interstitial fluid glucose concentration and the blood glucose concentration are very

similar. Now, they're not always the same, and that's a subject of research in itself, but they're often about the same, and that's just the first approximation.

So these are some methods that are being used now to pull out interstitial fluid. You can apply current, and that method is known as reverse iontophoresis. You can apply laser to drill a hole, in effect. That's called microporation. You can use ultrasound, such as what Santra Medical is using. We saw a picture of that. That's referred to as cavitation, creating a space between cells and the interstitial fluid sort of comes up to the surface.

You can puncture the skin with a very fine needle. You can abrade the skin surface with powder. You can dissolve the lipid barrier of the skin on the surface with chemicals. You can apply very strong suction or you can penetrate the skin with a fiber optic filament. And these methods are all ways of disrupting the skin, but not going so deep as to draw blood.

This is the last method that I mention. This is a technology that we're about to be testing at Mills Peninsula Health Services in which you have a fiber optic filament that's inserted to measure epidermal interstitial fluid glucose, and this method just stays in the epidermis and through an optical fluorescent reaction on the surface. You actually send light down the needle it fluoresces according to how much glucose there is, and you're measuring the fluorescence within the needle.

Okay. I've talked about one type of emerging option, which is noninvasive and minimally invasive monitoring. Another option that's available for patients now is alternate site blood glucose testing.

This is one of my patients about to do violence to herself, and imagine if you had diabetes and you had to check yourself four times a day, or maybe even seven times a day. This would really be a drag.

Imagine if you could check a blood sugar, but you didn't have to use your fingertip, if

you could go to a place where it just doesn't hurt as much. That's known as alternate site blood glucose testing.

The status is now that five of the six major manufacturers have products approved for alternate site by the FDA, and I know that the sixth company is working on it, and we'll probably hear something from them any time. So basically I expect that at least five, probably six of the six will have products approved by the FDA.

Clearly there's less pain than a fingertip site. As far as when is it okay to check an alternate site, there's a question of the lag for two hours after meals and during hypoglycemia, which means that as the blood sugar is rising and you know it's rising if you do fingertip blood glucose levels, it doesn't rise as quickly from the alternate site.

So if you check the blood sugar at the route of the alternate sites, using the forearm or thigh, within the first two hours you might think it's not as high as it really is because of this

This is one of the first people in the world to have an alternate site. He's one of the first 50 people. He's one of my patients who also gave me permission to show his picture here today, and as you can see, he's not really sure if this is going to work out, but he's being tested on the forearm.

This product is so historic in the field of alternate site testing it has actually already been on the market and gone off the market, but this is the first alternate site blood glucose monitor. It was called the Atlast by Amira Medical, and Amira Medical was later purchased by Roche Diagnostics, and one of the things Roche did was take this product off the market.

But this is the beginning of an era of alternate site testing.

Now, the next option that has become available for patients is continuous blood glucose monitoring. There are four products that one can use in the world for continuous blood glucose monitoring or continuous glucose monitoring. Two of

them are available in the United States and Europe, and the other two are available only in Europe and are not FDA approved for use in the U.S.

These are the products, and I'm going to say something about each of them. Starting with the continuous glucose monitoring system and the Glucowatch, the Glucoday and the Pendra.

So first, the continuous glucose monitoring system which has recently been upgraded to a second generation product. Now it's known as continuous glucose monitoring system gold And this is manufactured by Medtronic MiniMed in Northridge, California, and it consists of three parts.

First is a sensor that goes under the skin, and it can sit there for 72 hours in the subcutaneous tissue. There's a little wire from it, and this wire is connected to a monitor that stays out of the body. It looks like a pager, about the size of a pager, and that stores the data. It stores the data but does not project the data in real time, just like a 24-hour Holter monitor stores the heartbeat data but does not tell the patient

what the heartbeats are at that time. And it could be, in future generations we could see real time data, but what's on the market at this time is more like a Holter monitor.

And then you can take this monitor and put it into a docking station, and then link it to your PC to download the data, and what you get is a picture that looks somewhat like this, which each color throughout the day is a blood glucose level, and what you look for is certain times of the day when there's a pattern when things look really high, like maybe at this time of day here, or maybe when they look really low, like around this time of day here.

And thanks to some technology that has to do with smoothing, Medtronic MiniMed has recently found a way to connect the lines at midnight so that there's less of a disparity.

Next I'm going to talk about the Glucowatch G-2 biographer. Glucowatch is well known among diabetes circles. We're on our second generation device now. This is what it looks like.

It could be useful for a person at night because it has an alarm to wake them during hypoglycemia. This is manufactured in the county I live in, San Mateo County, by Cygnus in Redwood City.

So what you see here are three types of input. This device tells you the time, which is in green. It tells you the blood sugar level, and there's a trend arrow, and this trend arrow to me is a nice idea. It's really easy to make, but what you see is if your blood sugar is sort of borderline, and it's on the way down, it's really important. Now you've got to eat or take some action, or conceivably if your blood sugar is high and it's on the way up, it's time for some extra insulin.

I should point out that under the terms of this product being cleared, it's not cleared for use such that you can take the blood sugar reading and act upon it. For example, if you see a 110 and your doctor has said when the blood sugar is under 120 you've got to eat and you're seeing 110, does that mean now you should eat because the doctor said

under 120 you should eat?

No, because the terms of the clearance, what's said, is that this information, if you're going take some action based on the reading, you have to go check yourself with the traditional blood glucose monitor and use that information to decide what to do.

So it tells you, in effect, if the number looks alarming that it's time to check yourself with the traditional blood glucose monitor. I think this was possibly a step to give a patient an extra measure of safety because this is an early device that measures glucose in a nontraditional way, and by putting in this extra step, if for some reason the device was not giving you an accurate reading, you're still protected because you're going to go out and do a traditional blood glucose reading.

Here's how it works. This is a cut-away. On the face you have a display unit in purple. Now we go to the bottom, and what's happening is that the electrodes in yellow create an

electrical current. The current pulls salt from the skin toward the surface. The salt carries water that's dissolved, and water carries glucose that's dissolved within the water.

So what you're pulling up, in effect, is a diluted form of interstitial fluid. The glucose is trapped in these glucopads, also known as autosensors, and a chemical reaction occurs with the biosensor, and you get a glucose reading.

The way this device operates is there's a two-hour warm-up. You put it on and it gives you no readings. Then after the two hours you still need to do a single calibration every 13 hours, which is how long it lasts. That is, you get readings for 13 hours. It will deliver six glucose measurements per hour that you can read. So every ten minutes it gives you a reading. It has a programmable alarm for panic values, such as that woman who was sleeping. If the blood sugar gets below a certain level, it will make a noise and wake her up.

Excessive sweat cuts off the

measurements, and it uses a triple A battery every 13 hours. This is a product that's approved in Italy. It's a continuous glucose monitor known as Glucoday. It uses a principle called microdialysis in which interstitial fluid is sort of rinsed, and the fluid that comes out contains glucose and using a proprietary formula, the concentration of glucose in this rinsed fluid is supposed to be proportionate to glucose in the interstitial fluid, which is supposed to be proportionate to blood glucose.

Another product which recently received clearance in Europe is the Pendra. This is an interesting device by Pendragon Medical in Switzerland. This is actually a noninvasive monitor. So there's no fluid. The skin doesn't become wet underneath, and it uses a method known as radio frequency impedance, and it sends a radio wave to the blood.

And it turns out that, according to the Pendra, that if the blood glucose level changes, that changes the shape of red cells, and that changes the dialectric properties of red cells and

changes the impedance. So they're measuring glucose indirectly by this method.

I made a list of some other promising technologies for implanted, either minimally invasive or invasive, monitors that will be used as continuous sensors in the future. I think any one of these on the list could be the next continuous sensor that we're going to see.

And the type of signal that they read generally is either an electrochemical signal, such as an enzyme sensor under the skin, or it measures optical energy.

So when we go through these, I see first you can have a microdialysis catheter subcutaneously. That's what the Glucoday uses, and recently Roche Diagnostics has announced that they're very interested in this type of technology as well, microdialysis.

Viscometry is a method in which you're rinsing interstitial fluid out as you would with microdialysis, but there's sort of a catch to it, is that you're using a solution that contains dextran

and Concanavalin A, and in effect, the higher the glucose concentration, the more glucose will be pulled off the dextran onto the Con A, and the viscosity is less, vice versa.

So, in effect, high glucose is low viscosity. Low glucose is high viscosity, and that's a viscometry method. This method has been developed by Disetronic in Switzerland, and Roche Diagnostics recently acquired Disetronic, and we'll see what happens to viscometry.

Another method could be to implant a Fluorophore, an agent that fluoresces under the skin or put a tatoo under the skin and then you interrogate this agent with light. That could be a continuous monitor.

And there's a company near here in Germantown, Maryland, called Centers for Medicine and Science, that's working on this technology.

You could use an enzyme tipped catheter implant, which is essentially what the continuous glucose monitoring system gold uses, and there can always be a new generation by Medtronic MiniMed or

some other company, and this could either e a subcutaneous device or an intravenous sensor, and here again Medtronic MiniMed is working on one and so is Animas in Pennsylvania.

And Animas' method is using a near infrared spectrophotometer intravenously, which is pretty interesting. The idea is that you've got a noninvasive type method, which is shining light, but they actually have the light and the receptor so small and so close to each other that they could implant that as a unit into a blood vessel.

Okay. The last area where there are more options in terms of metabolic monitoring are integration. I can tell you at the American Diabetes Association meeting, which was in New Orleans last month, for the first time I was struck by a trend which is integration between blood glucose monitors and insulin delivery systems.

People are talking about it, but it was everywhere you looked at the ADA meeting.

Now, there's two kinds of integration. There's the mechanical integration where two

different systems are located next to each other, but they don't necessarily work together, but even more important is functional integration where they actually function together.

Now, the first mechanically integrated system was known as the InDuo, and when it came out, the manufacturers, Novo Nordisk, which is an insulin company and Live Scan, which is primarily a blood glucose monitoring company, asked the question, "How did you manage before InDuo?"

And they showed this mess of stuff that you have to deal with because now they came out with the first ever -- I insert the word "mechanically" -- integrated blood glucose monitor plus insulin delivery system, but there's no sharing of data. This looks like a blood glucose monitor on the outside, but it's a shell. When you lift it up, it contains an insulin delivery system, which is basically a fancy pen system for delivering insulin.

So it contains both, but there's still just two things that are linked together. They don't necessarily work together.

The second mechanically integrated blood glucose monitoring plus insulin delivery system was created by BD. They call this the Latitude diabetes management system, and this system contains various features that a person with diabetes would need, a glucose monitor; this is in millimoles per liter, not milligrams per deciliter, and it contains a lancet, and it contains an area where you can put a pen.

So here, again, these are mechanically integrated, but not functionally integrated. Now we're getting into functional integration, and these are four recent alliances that I've become aware of -- just some of them recently, some of them still not very long ago. I've listed them from top to bottom according to the size of the insulin pump company.

Medtronic MiniMed is the largest insulin pump company, and they've recently formed an alliance with BD, which is a blood glucose monitoring company.

The second largest is Disetronic out of

Switzerland. They've recently not just formed an alliance, but been acquired by Roche diagnostics. That's definitely an alliance.

The third largest, Animas from Pennsylvania. They formed an alliance with Lifescan.

And then the fourth largest, which is pretty new on the market in insulin pumps is Deltec in Minnesota, and they formed an alliance with TheraSense.

I'll say a little bit more about what each of these alliances consist of. This slide was stamped on the upper right corner "FDA Clearance July 7th, 2003." So as Dr. McClellan stated, we now see that here we have FDA clearance for a combination product which is a blood glucose monitor developed by BD and MiniMed called the Paradigm Link Monitor. Here's the person sort of on the run holding their blood glucose monitor, and by radio it sends a message to the insulin pump that the person is wearing, the Medtronic MiniMed Paradigm 512 pump.

So now for the first time you have an

FDA approved combination product which is functionally integrated. The glucose level is projected into the pump.

Medtronic MiniMed then took it even one step further in terms of integration, and they created a type of software which they say does -- they call it diabetes math. It tells you based on -- you know what's your blood sugar now, and it tells you there. You know what you want your blood sugar to be. You program that in. You know what you're about to eat. The device is pre-programmed with how sensitive you are to insulin and how sensitive you are to calories.

And with that information, as well as one other factor which is how recently did you take some insulin, it will tell you what type of a bolus of insulin you need to get your blood sugar down to this target level.

And they actually did a study which they published in Diabetes Technology and Therapeutics in June where they took some experienced people with diabetes and said, "Okay. You must know how much

regular insulin to give yourself at a meal, and so half of them, use how much you think you should use. The other half, don't use what you think you should use. Use what our diabetes math formula tells you."

And it turns out that the control was exactly the same, but from the standpoint of the manufacturer, that was a good thing because there are a lot of people with diabetes who aren't so experienced and have a lot of trouble figuring it out, and the machine --the software-- did as well as what an experienced person could do. So that's a promising sign as far as integration goes.

Now, Disetronic and Roche, what do they have planned? This is a part of a press release on May 2nd, after we see the Roche acquire Disetronic. By combining the two businesses, Roche will be able to offer comprehensive diabetes management solutions from blood glucose meters for self-monitoring to sophisticated, programmable insulin pumps that allow patients to continually administer insulin doses according to their individual needs.

So to me, this sounds like they are

getting ready to integrate their pumps and their glucose measurement systems.

Now, Animas and Lifescan. I'm not sure exactly what they're doing together, but I can tell you that each company has a link to the other on their Web site and to no other diabetes company. So that tells me something is going on.

Finally, Deltec and TheraSense have created a product which is not FDA approved, but people form both companies are optimistic, and what you have here is an insulin pump made by Deltec and then clipped over it, this basically just looks like a little holster or clip. It's actually a TheraSense Freestyle blood glucose monitor.

So we look at this from the front and from the back. So one thing that TheraSense is good at doing is creating blood glucose monitors in different shapes, and they have created a monitor that basically looks like a clip, and you stick the strip in the bottom of it, and you get a reading here.

So I'd say from a design standpoint this