structures are just too susceptible to the peptidases, and all of those severely limit the application.

Normally we're not allowed to show animals in distress, but you know, this is not too distressful. This would be the same thing that you would see in a human being. You've probably heard that the average diabetic may inject themselves 40 or 50,000 times during a lifetime. No one likes that.

One of the things you probably don't hear enough about is the fact that there are so many borderline diabetics or diabetics who just plain refuse treatment because they don't want needles, period.

And that actually is a very important segment of population, in my opinion.

Well, why don't you just swallow it? Well, with the bioavailability orally of growth hormone, you'd need about $120,000 a day and quite a bit of eating. That's not very practical.

So why not inhale? People say it's too

hard. It takes too much education, whatever. The fact of it is an 18 month old can use an inhaler, sometimes even by themselves.

Just to back up a little bit, too, on what is the lung, the lung has 23 generations of airways, and those airways' surface area would be the equivalent of that towel thrown on the tennis court, and the tennis court would be the equivalent of your lung surface area, and if you talk about the volume of lung surfactant, it's about 30 mils.

So when people say they're worried about high doses to the lung, if you have a very dispersable, well aerosolized product, that whole product can actually use that whole lung, and you can imagine that a milligram or three milligrams -- whoa, five minutes? He's vicious. Okay. I'm going to have to skip some. I think the introduction went into my time.

(Laughter.)

DR. LEACH: So you can see that even though you're talking about a lot of surface area, and sometimes you're talking about three milligrams,

four milligrams of drug, when you imagine those little particles spread over that tennis court, it's really not a high concentration.

In fact, the concentration you're given by IV or Sub-Q is much greater than this.

Okay. I'm going to have to skip some here.

The rule of thumb though is that for about two to five percent of the IV dose actually reaches a lung. That's not very efficient, not very attractive.

Five minutes. So I'm going to have to skip some of this.

Let me give you a couple of examples here. Leuprolide, which you've already heard about, is very, very limited by its side effects. We wanted to see if we could get inhalation bioavailability to match an IV dose in this, and in fact, this is a human clinical study, and I'm sorry it didn't show up that well. But we showed that we could do a dose by IV injection and match that dose by inhalation very well.

As you know, the side effects can be severe, headaches, and especially with these implantable devices. Once you get them implanted, you're going to live with the side effects for a very long time, as opposed to inhalation product where you can titrate yourself down or even stop temporarily.

PulmoSpheres are our version of what you've heard about this morning. They're wonderful materials. They're hollow. They're porous. They're ultra low density. They're able to get to the deep lungs so that you can take advantage of that huge surface area.

They are actually made of lung surfactant themselves. DSPC and DPPC are natural components of the lung excipient.

And so what are the preclinical issues here? Well, again, there's larger lung concentrations that are going to be seen from leuprolide. Lung doesn't normally see leuprolide, but again, you get big doses spread over that tennis court, gives you reassurance that it's not going to

be too bad. One must certainly do the work anyway.

There's the antibody question, and then there's the excipient question here. That's why people choose excipients that are very compatible, biocompatible.

Okay. One of my personal favorites I want to spend a minute on is antibiotics for lung disease. It's so unattractive to give an antibiotic either orally or IV for a lung disease that I'm surprised that we haven't gone a lot further with inhalation antibiotics than we actually have.

Here's an example of one that's actually on the market. If you look at the blue lines here, they're what normally happens when you inject it by IV. You can see that you get a nice, good curve here.

But when you go up and look at the lung, the lung values here -- I'm not sure it's showing up. My angle is not good here -- it's about 20 micrograms per gram of tissue. Okay? This actually is not too much approaching the MIC.

Now, if you look at the lung lavage, you

can see they're almost not detectable. Well, you can take that same dose and give it by the lung and you get none in the plasma. You get a fairly significant amount in the lung lavage, which means that it's on the mucosal side where the actual bug is, and a huge number in the lung.

In fact, there is a line broken here, and this number is 1,500 versus about 20 on this line. So you can see that if you just have a good powder, and I emphasize you just can't put these things in nebulizers and expect to get these kinds of results because they're notoriously inefficient. They don't get to the deep lung, et cetera.

If we go on to a more sophisticated study in dogs, this is an actual tox. study, PK study and whatever kind of name we could put on it to get to our endpoints. We see the same thing. We could get a nice, good dose response relationship. We get plasma half-lives at 28 hours, and we get lung tissue half-lives of 19 days.

And I think the important point here is we can get four orders of magnitude difference

between lung and plasma. So the hypothesis here is that if we want two to three times the MIC, the plasma levels are likely to be undetectable, and the plasma levels, again, are the limiting side effect of this particular drug, and so those have the potential of going completely away.

Skipping some of the good stuff, I added this in because of the mention of PEG. PEG insulin is a very important thing right now. If you have a long acting PEG, then you can provide basal levels to diabetics, and I think most of Type Is and about 20 percent of Type IIs actually require some basal injection.

And even when the inhaled product comes out, they're still going to require that unless we come up with a longer acting. We think PEG is one of the ways we can do this. PEG is a really interesting. They're very, very safe. They've been in many approved products, and the PEG is actually a long chain here, and this would be the drug.

And not shown here is the hydrodynamic diameter. There's actually about five to ten times

the molecular weight of water that actually surrounds this. So it protects it from the immune system. It also protects it from degradation in the lungs, et cetera.

And I'll just show you one piece of data on that, and that is glucose suppression. Again, I don't have time to go into a lot of details. For those of you who know about insulin and know about glucose suppression, if we give normal insulin, we normally can suppress glucose that would go down to these sorts of levels, and it lasts about two hours and then comes back up. You saw a similar graph earlier today.

If we use PEG insulin here, then we can go down, suppress it, and stay out here. And we've gone out to eight to ten hours, and we presented this at the ADA meeting about a month ago. So we're very hopeful that we can come up with a pegylated insulin that might last as much as ten hours and get people through the night.

Okay. In summary, a route changed inhalation can offer fast onset. I didn't get a

chance to really talk about that, but, for example, nicotine by inhalation only takes six heartbeats to reach the brain. So things like fentanyl might be very interest for instant relief.

Higher bioavailability than some other routes. Freedom from ejection, less side effects. The preclinical requirements should be unique to each new change in route. I don't believe there's ever going to be a cookie cutter approach to these issues. It needs very close work with the regulatory authorities.

Preclinical programs should stress the exploration of known differences, not unsubstantiated speculation or not what's particularly in vogue. These things add up to a fear of the unknown and unreasonable preclinical and clinical requirements that keeps many new drugs from really happening, especially for the non-blockbuster category drugs.

I can't tell you how many conversations we've had with drugs that we know we can make significantly better or we can give by the pulmonary

route and really improve and meet an unmet clinical need, but if they're in the 50 to $100 million range, nobody wants to touch them. There are many, many, many like that, and it's really heartbreaking to know that we could do such a better job than what's out there, but the economics are driving it.

And the fear of the unknown, which is my last slide.

(Laughter.)

DR. LEACH: Thank you.

(Applause.)

DR. HUSSAIN: Thank you for the excellent presentation. I'm sorry I had to show you the five minute page.

The next presentation is entitled "Protein Delivery from Implantable Devices: Challenges and Opportunities," to be presented by Bill Van Antwerp, Vice President and Chief Scientific Officer of Medtronic MiniMed.

DR. VAN ANTWERP: Well, thank you. I'd like to thank Miriam and the FDA for inviting us here to tell you a little bit about our view on

protein drug delivery.

You've heard a lot this morning about things that might happen in the future. Bob Langer, in particular, gave us a vision that's incredibly long seeing.

I'm going to tell you a little bit more about the grunt work that you have to do in the lab to make some of these products possible.

Okay. So why protein drugs and why protein drugs and devices? Proteins are becoming increasingly important for a variety of disease states: diabetes, which is near and dear to our heart and everyone else's; cancer; cardiovascular treatments; inflammation; HIV/AIDS; Hepatitis C, for example.

Those are drugs that are now coming or now approved. There's a variety of drugs from a variety of companies also coming on line that are proteins. Proteins need delivery, as we have all heard. They need delivery. They're not very bioavailable. They get denatured. They get hydrolyzed. They get degraded by enzymes, and if

those escape some of those routes, they're not absorbed very well either due to their size or due to their polar or charged distribution.

There's a variety of companies developing novel technologies. We just heard about pulmonary delivery. There's a variety of depo injection and other technologies. We're going to talk about the old fashioned way, which is basically delivering through the skin through a subcutaneous or interperitoneal infusion using mechanical devices, pumps.

Bob Langer showed you something like this slide earlier. This is a classic case where we have a drug that has about a six-hour half-life, and if I deliver it via injection and then I have in blue here a therapeutic range, I need to give another injection 12 hours later when I'm just at the nadir of activity. Well, I have to deliver 14 times as much drug.

More importantly, the side effects are often due to the peak concentrations. Enzyme activation is incredibly important. In fact, in

Colin Denney's group at M.D. Anderson he's shown that high concentrations of drug actually deactivate enzyme or activate enzymes that deactivate the drug, and I can deliver via mechanical devices drugs with a perfect matching of the drug to the therapeutic range.

Today parenteral delivery of drugs are done via two old routes, IV administration, subcutaneous injection. Two routes that have had some success, continuous subcutaneous infusion via mechanical pumps and continuous interperitoneal infusion, both of these mostly for insulin, but they've been used for a number of other compounds as well.

And we've heard a lot about subcutaneous depos, PLGA microspheres, PEG attached peptides, micro emulsions, pulmonary delivery, and also there's some new routes, intrathecal and intraparenchymal delivery.

Medtronic has a significant business in intrathecal delivery of small molecules, morphine and baclofen, although just recently we're starting

to look at those routes to get drugs into the brain, cross the blood-brain barrier using proteins.

Well, what are the challenges? Well, Bill Clinton said it about the economy. Here I would tell all of you involved in drug device combinations that it's the formulation. Formulation, formulation, formulation.

Old challenges, formulation stability, chemical stability, clearance issues in the body once you inject it, but when you start to give drugs by mechanical devices, you run into two new problems.

One is physical stability. If you pull a syringe full of insulin out of a bottle and I inject it Sub-Q, I don't have to worry too much about the physical stability of that insulin.

If I put it in a mechanical device, I have to worry a lot. I also have to worry about some PKPD issues because now I'm giving it continuously in a trial that we just finished, the Phase I trial. We had a dose escalation study planned. It turned out to be a dose de-escalation

study because when I gave the drug continuously, it was much more effective than we had thought by continuous or by multiple injections.

We found that patients had to down-dose rather than up-dose, and we have to think a little bit about toxicity in a different way. This is not systemic toxicity, but if your formulation isn't right, we need to worry about localized site reactions. If I have got an injection catheter that's in the subcutaneous tissue and it's supposed to be there for three days, I have to make sure that the formulation of the drug is suitable for those three days of delivery.

Regulatory hurdles, let's not reinvent the wheel. We build devices. The device physics are what they are. If we build a pump, it turns out every time we want to put a new drug in the pump we have to prove that the pump pumps again, even though we've shown in the laboratory that it pumps with a wide range of viscosities. It's always an indication that we have to prove that the pump pumps again.

The same thing is happening with drug chemistry. We're developing a prefilled insulin cartridge. The insulin degradation chemistry has been well known since the late 1920s. Yet we have to show that the impurities in our insulin are exactly the same as the impurities in all the other insulin formulations that have ever been developed.

The same with drug packaging. We try to use for pumps the kind of packaging materials that people have been using for the drugs for a long time, but again, we need to show stability.

There are, however, two areas where we need to pay much more attention. One is pump-drug interactions and drug physical stability. What we like to say in our laboratory is that when God invented insulin, She didn't design it to be stable for 90 days at body temperature sloshing around in a metal can.

These are the kind of things that traditional drug systems don't need to think about. We need to think about physical stability.

Stability in pumps has two components:

chemical stability, which in our hands looks very much like stability in primary packaging. We don't see chemical changes in formulations that we don't see at the same temperature in primary packaging.

Physical stability is important. Why is it important? I'll show you in a minute some results from some studies, but physical stability generally leads to things like soluble aggregates, Soluble aggregates are well known to lead to antibody issues that you don't see, for example, with noncontinuous infusion.

There have been a wide variety of measurements of physical stability in the protein business. Every protein company has five or six in their labs. None of them seem to give you exactly the same results, at least in our hands, and I want to propose some testing that I think makes sense in a lot of situations.

People have looked at turbidity, concentration changes, fluorescent spectroscopy, microcalorimetry, and a whole variety of other things.

As I said before, chemical stability determined by the molecule, by the formulation. One important point to note, that relatively straightforward formulation changes can affect stability, and what we have seen in devices ranging over a wide range of molecular types, interferons, insulin, interleukins, and a variety of peptides, large and small, is that the stability in the device is pretty much the stability in the primary packaging.

Physical stability, however, isn't. It depends on a number of things. Probably most important: the physics of the device, whether they're sheer or compliance in the system; what the materials of contact are, Teflon, titanium, polyolefins, silicone oil. All of these are common in medical devices.

Agitation is incredibly important, as is body temperature storage.

We believe that in physical interactions there are a couple of steps that are important. The first is absorption. The next is denaturation,

typically on the surface, and we believe that a lot of the story in terms of physical stability of proteins and devices can be told by looking at partially unfolded intermediates.

Tony Fink's group up at U.C.-Santa Cruz has been a leader in this idea, and we concur with some of what he has done. Once we get these partially unfolded intermediates they lead to aggregation on the surface, which then leads to aggregation in solution.

We have a model here. Part of this model was originally proposed by Bob Langer many years ago now, but we have a protein. It sticks to the surface, then unfolds, falls back into solution, forms aggregates, and the model is autocatalytic.

And we test this in the laboratory now. Five years ago it took six months to a year to understand all of the physical stability of a protein in a pump. We can now test it in a few hours or a few days.

And basically this is the autocatalytic curve. We put the protein in a 96 well plate with

some Thioflavin T. Thioflavin T is a fluorescent molecule that only fluoresces when it's bound to aggregated proteins.

We look at the fluorescence as a function of time, and we curve fit this to the autocatalytic curve model. You see that the correlation coefficient is .99, which is quite nice.

What's the point of all this testing? Well, the point of all this testing, one point here is to look at the physical stability in contact with a number of materials so that when you're designing devices you always have to design with materials that are available. You know, FDA doesn't like to see new chemical entities particularly that might end up in your drugs.

So here we've taken a formulation of insulin and compared it in the same experiment with Teflon, polyethylene, glass and titanium, and what you see is that the Teflon is by far the most susceptible to aggregation, whereas glass and titanium are quite nice.

And this difference here, this

difference between 50 hours and 150 hours, we have good correlation to stability in clinical testing in pumps.

Similarly, and this is the formulation issue with a different compound, different formulation, we have two drug substances, a new one and an old one, and we formulated them two different ways. In one case we simply dissolved the protein at high pH and then pH'ed it down to pH 7.4, and then the one we call low pH, we took the drug substance, dissolved it in acid and then took it up through the PI to the appropriate pH.

And you see that even though the end formulation is exactly the same by any chemical tests that we can do, the physical stability when I start out at low pH versus when I start out at high ph, this is a factor of four or five more stable, which has significant implications in the clinic.

Okay. So where does that leave us? Formulation, formulation, formulation. We're a device company. We're not a drug company. All of the products that we put in our devices come from

biotech companies, typically not big PhRMA, although insulin is obviously not the case.

If you want to talk to someone about devices, if you're a PhRMA company or if you're a device company wanting to talk to PhRMA, start with the formulation. There are multiple interactions that you need to study. Control of the material interface is the most important thing, and what's very important from the regulatory standpoint, device design and formulation need to work together and be regulated together.

We always talk about our devices breaking proteins. This is a picture of a protein that actually broke the device. This is a seal. This is a titanium seal, and you can see the titanium here. This is a deposit of insulin crystals that formed on this seal, and this was ten years ago now, on an implantable pump, and you see that this seal worked perfectly fine, except where this crack was.

This crack allowed actually insulin to flow out. The seal no longer worked. This caused

us a lot of headaches. It turns out that it was a materials and formulation issue which has now been solved thankfully.

So in conclusion, interactions need to be managed. They need to be understood. Pump design and formulation need to work together. Combination product components can be evaluated separately using historical data. We have pumps. We know how they work.

However, we need to pay appropriate attention to the drug-device interactions. Those are the things that are critical.

And when I talk about "we," I really mean "they." This is the Protein Formulation and Stability Group at Medtronic MiniMed. They only let me in the lab now to get coffee for my coffee machine.

(Laughter and applause.)

DR. HUSSAIN: Our next topic is developing a local drug delivery combination product for postoperative atrial fibrillation, preclinical challenges, by Dr. Kevin Skinner.

DR. SKINNER: Thank you very much, and, Miriam, thank you for organizing this conference.

We've been working on this project for two years. So I'm going to discuss the development process, and at this point in time we've gone from concept to a bench research level, and we're at a preclinical research level.

And the concept actually came from clinicians and marketers, and they brought that idea to us. We started evaluating this concept of marrying biomaterials with an old drug entity called amiodarone, and then we took it into preclinical research to get a proof of concept.

In the near future we'll take it into a preclinical development phase, which will enter into a history design, and then move it into the clinic.

So postoperative atrial fibrillation, it's a kind of tachycardia that you see in patients following CABG and bowel surgery. It happens around 20 to 30 percent of the time, and usually happens within three to five days, but it can happen up to two weeks following surgery. It increases the

length of stay for the hospital or for the patient up to 1.5 days, and people have assessed or have followed this from an economic standpoint, and it can cost the patient about 8,000 more dollars.

You get a decrease in cardiac output. You get an increase in stroke due to stasis in the atria, and there have been prophylactic treatments, but they're not widely accepted. Amiodarone is a drug of choice for treating postoperative atrial fibrillation, but it requires at least for oral dosing seven days prior to surgery, and if you use the IV formulation, you have some severe side effects.

So amiodarone is probably the most widely used antiarrhythmic for clinical use. Its label indication is for ventricular tachycardia and for ventricular fibrillation and super ventricular tachycardia. However, it is used off label for atrial fibrillation. In fact, it's the most common use of or amiodarone is the most common use for AF.

It's a Class III drug, which means that it increases the action potential, and increases the

effective refractory period.

But, as I said, one of the drawbacks with the drug is it has high toxicity for pulmonary, and it also causes bradyarrhythmias following loading doses. The systemic doses you actually have to load up to gram quantities within the first week, and then it tapers down to between 800 and 400 milligrams.

So the thought was: could we deliver that drug locally? And there was some basic research done by Ayers and Zipes, where they locally delivered the drug into the pericardial sac. However, they had to load it for three hours, and they looked at several doses. They looked at the EP parameters following the administration of amiodarone locally, and they measured myocardial drug levels.

So what we have here is we have both the atrial refractory period and also the dose level, and so what you see is increasing from the control up to the five milligram dose you get an increase in atrial refractory period and also an increase in

tissue levels.

And the effective doses or therapeutic levels that they saw in the tissue was between 20 and 120 micrograms per gram of tissue, and this is the data that you see in humans, patients that have died, and they have posted their tissues and have posted the level of amiodarone. So, you know, that's the therapeutic level of drug.

And in these animals they only had a small amount of trace drug that was found following the dosing for three hours. So the thought was could we find a biomaterial that we could put amiodarone into it.

Genzyme had a collaborative research with a company called Focal and subsequently acquired the company, and the technology is a bioreabsorbable PEG based hydrogel. It's actually approved in the United States and in Europe for lung sealants for pulmonary leaks, and in Europe it's approved for dural sealants. It's tissue adherent. It's compatible with drugs and biologics. You spray it on or you can drop it on as a liquid and you

photopolymerize it with light. The product can be tailored to whatever application you'd like to use it for.

So the questions we wanted to answer were could amiodarone be delivered via this tissue adherent hydrogel and could we get effective doses, and can we reduce the amount of drug levels, and would it not be systemically found?

And can these drug levels cause an EP effect that would prevent AF?

So the product characteristics were could it adhere to cardiac tissue. We have a pumping structure. So that was a challenge for us. Could we deliver the drug locally? Were we able to reduce the level of drug? And could we deliver it up to 14 days? And was it compatible with cardiac tissue?

So before we even went into doing animal studies, we wanted to make sure that there wasn't a drug-device interference or a device-drug interference. So we wanted to make sure that the hydrogel did not affect the amiodarone. So we did

HPLC mass spec analysis and demonstrated that the drug was not affected by the hydrogel or its individual components.

We also made sure that the amiodarone didn't affect the in situ polymerization of the hydrogel or other properties of that hydrogel, and we could load up to five percent of amiodarone into the gel without affecting those properties, and then we demonstrated in vitro release that we could get up to two to three weeks of drug being delivered out of that hydrogel, up to one percent of the amiodarone being loaded into the hydrogel.

So in the first study that we did preclinically, we implanted the hydrogel amiodarone at a half a percent and one percent onto the canine heart. We came back seven days later, looked for levels of amiodarone in the cardiac tissue and also its active metabolite desethyl-amiodarone, and we also looked at other tissues in the body, lung, kidney, and liver, and also urine and blood, and then we observed for any adverse events in animals.

So after seven days at the half percent

we got around 64 micrograms per gram of tissue in the half percent loaded gel, and the one percent gel gave us around 230 micrograms per gram of tissue.

The gel itself had only eluted only 30 percent of the drug at day seven, and we found four to six percent of the metabolite desethyl-amiodarone in the treated tissue, and there were no measurable drug levels in the lung, liver or kidneys. We did see some in the cardiac pad around the pericardium, but it's known that amiodarone, because it's fat soluble, will reside there. And there were no adverse events seen in any of the dogs.

So our next study was, you know, we can deliver the drug, and the amount of drug that we can deliver, would it have an EP effect on that?

So we looked at four groups: just the hydrogel itself, the hydrogel loaded at half a percent and one percent, and then we did a surgical control group.

And we measured EP parameters preoperatively, postoperatively, three to five days, ten to 14 days, three to six weeks, and collected

the tissues for drug level.

So what I have here is a chart that shows pre-op. Basically there's no difference between any of those groups.

Immediately after implanting the hydrogel or the hydrogel and drug, you see an elevation in EP, but the sham group also shows an elevation. So just the act of surgery increased the atrial refractory period, but by day three and five we see a significant increase in the treated group of almost a 50 percent increase in the EP in the treated group, and by day 14 you see the elevation of the EP relative to the control group, and we also see the effect out to three weeks.

And then when we harvested tissue at three weeks, we had therapeutic levels of the drug within that tissue.

So what we had shown in the preclinical research aspect of this project is that we're able to deliver amiodarone to the cardiac tissue at therapeutic levels, which is significantly lower than IV and PO routes. As I said previously, you

have to deliver gram quantities of amiodarone orally or milligram quantities IV. But for us, we were delivering milligrams, 16 milligrams, 32 milligrams, and we were delivering it once over a three-week period.

And all of those studies that we have done so far have shown no systemic levels of the drug other than where we placed the material.

And the product has been well tolerated in all of the animal studies, and we demonstrated that we were able to elevate the effective refractory period, which is indicative of the proof of concept to reduce the incidence of AFIB.

So where are we today? We're getting ready to plan the preclinical development strategy, and one is to leverage the existing data from FocalSeal. It has been approved in the United States and also in Europe, and the amiodarone has been approved for IV and oral formulation, and there's a generic form out there already.

So what we'd like to do is bridge those existing data that's out there and just do studies

that are necessary to really evaluate it for the specific use we're using.

In this chart, you know, when we were coming up with a strategy, we were trying to figure out, you know, was this going to be ruled a device or is it going to be ruled a drug, and somebody in our regulatory department came up with this cartoon.

And so if you look, what you have is the drug, the potential drug, and the way of delivery, and what you're looking at is a generic drug which is amiodarone or a new indication or a new drug entity, and if you, you know, look at how it would be delivered, whether it be chemically modified or would it be a depo effect or does it also have a device action.

So when we talked about drug eluting stents today, you either can look at it as a dip coated stent where it was a generic drug and it had a device action and it was ruled by CDER or whether it's a drug coated stent with a polymer that's being ruled by CDER or, in our particular situation, we have a generic drug, and it has a depo effect. So

it's being ruled by CDER.

So, you know, what are the bridging studies that we think we need to do? One is to look at the long-term degradation of this product on the cardiac tissue, and what are the acute toxicity issues of placing a biomaterial on the heart with the drug being delivered to the specific part of the heart?

And then what are the temporal drug deliveries? We've only looked at very short-term delivery of that drug, and we need to look at long term.

And then we would do confirmatory EP studies once we finalize the formulation.

So in summary, post AFIB is a serious unmet medical need which may benefit from the advances in therapeutics that are delivered at the time of surgery. The combination product of amiodarone and a synthetic adherent PEG based hydrogel shows promise for safety and efficacy in preclinical models.

We'd like to leverage prior studies and

perform appropriate bridging studies that should provide facilitated regulatory approval of this drug-hydrogel combination.

And this combination product is a good example of a device/drug combination with a primary pharmacologic mode of action.

Thank you very much.

(Applause.)

DR. HUSSAIN: Well, I was conflicted. I wanted to keep everybody else's time on the thing so I could use all of the time.

(Laughter.)

DR. HUSSAIN: No, what I'd like to do is sort of in some ways connect the various presentations that occurred this morning and also hopefully help set the tone for the afternoon discussion on regulatory.

Although I'm from FDA, I'm not actually taking a regulatory perspective, but more of a scientific, broad, almost an academic perspective. So the title of my talk that I've selected is different from what's in the brochure. I

essentially would like to sort of take a step back and summarize for you some of the discussions this morning and present to you the concept of quality by design, which I think is a preclinical opportunity to address many of the challenges.

In this session we had three wonderful presentations before mine, and we looked a preclinical challenges with respect to pharm tox and the need for doing additional pharm tox studies when there is a route of administration change or when there is a potential for change in exposure, and the exposures may lead to or trigger some safety concerns. And I think if there is a better way of addressing that, that would be a step forward.

And the second presentation was, I think, very important from my perspective to sort of highlight the importance of physical stability and in some ways I have sort of built some information on that from my perspective also. And I think physical stability is a gap in terms of our ability to analyze, do testing, which is proper and relevant, and I think there's a significant

opportunity for collaboration there.

And then finally we had a presentation on local drug delivery and how does one sort of not only start with in vitro methods that start screening interactions as well as moving towards a methodology that sort of demonstrates the local effect, and local effectiveness is also a significant challenge for us as we move forward.

So to sort of summarize some of the discussion and looking at quality by design concepts, what I thought I'd do is share with you the current FDA initiatives. This workshop is focused on the initiative as Dr. McClellan talked about, improving innovation in medical technology. This is the workshop sort of starting this initiative, but there are two other initiatives, and there are synergistic interactions between these initiatives, and I think hopefully you'll see a linkage between these two.

I would like to sort of put on my academic hat and use a very old slide that I used to use when I used to teach, and this was sort of an

evolutionary step in pharmaceutical products and process development, and I want to sort of use that as a framework for defining quality by design.

Pharmaceutical manufacturing, as opposed to, say, device manufacturing and so forth, essentially originated in the other pharmacy compounding, and it has moved over the last 30 years to more science and engineering based.

So now you can start talking about pharmaceutical engineering, and I think there is a big advantage of thinking of developing products from an engineering perspective.

In that vein, I think we have moved from dosage forms to now what we call drug delivery systems in the late '80s. And now we're moving towards innovative or more intelligent drug delivery systems, and I think that's the drug delivery systems and intelligent drug delivery systems which is essentially the focus of this initiative and workshop.

But in terms of, I think, quality by design, we have to take a step back and see how we

are developing these products and what impact does that have on efficiency of development and time to market.

Traditionally pharmaceutical development started with trial and error type of experimentations where it's often difficult to manage the multi-variables and the interactions between those variables. We moved to a more of design of experiments, more empirical statistical designs in the mid-'70s, but yet we have not moved to computer aided design, and I think we have an opportunity to start thinking in those terms, and it can have a very significant impact on not only the development time, but I believe on the regulatory assessment itself.

If we're able to move in this direction, I think we will have our resources focused on testing more creative options, and that's what I want to sort of convey with this slide at this point. The other aspects, I think, end product testing, a focus on testing to document quality as opposed to real time quality assurance also has some

bearing and is part of the other initiatives I talked to you about, but I will not get into that in detail here.

If you look at the traditional approach to formulation development, Professor Langer had a slide in his second to last slide, I believe, where he had a black box, and through strategic experimentation and so forth, if you notice the black box became transparent, then you could see inside the black box, and I think if we are focused on trial and error and being part of the art of product development, then I think we have a black box to deal with, and that poses significant regulatory assessment challenges and leads to questions which may not really be in the best interest of the development program.

So if you look at traditional dosage forms, a typical pharmaceutical focus would be making sure it's stable and then it's bioavailable, and we approach that formation development looking at drug and excipients, the physical and chemical properties to develop a formulation and then try to

understand the in vivo and in vitro attributes of those products that we develop and screen, and how are they absorbed and are they bioavailable or not?

So there are many aspects that sort of bring in the physics and the chemistry as well as the test methodologies or also the physiology that comes into consideration to develop a formulation which is bioavailable and stable.

But this is relatively simple when it comes to drug delivery systems. I think the challenges get confounded and have significantly much more than that, and typically I think the CMC and GMP considerations that I think we struggle with is to insure consistent quality and performance is the objective. How we design and how we develop specification for a given product, how do we manufacture and how do we establish manufacturing processes and their controls, test methods and shelf life are key challenges.

And then once we have an approval, you know, process validation, manufacturing under GMPs and making sure that the manufacturing remains

consistent are significant challenges, too.

Studies during development can have a significant impact on development time. Many speakers before me have touched upon that, but I think I'm talking about bridging studies with respect to bioavailability characterization from a chemistry perspective. So you have to address some of those, and in absence of good analytical methods that relate to in vivo of performance or to shelf life, it becomes very difficult to manage changes that are necessary during the development program, and the bridging studies can become very elaborate and can often be clinical studies themselves.

So unless I think we think of new methods, I think these are potential bottlenecks in the development program that I think we will face.

Post approval changes often is not on the minds of people who are focused on developing formulations and doing the clinical studies. But I think thinking about post approval changes is important. Change is part of life, and changes lead to improvement at the same time, but if you're not

able to change and justify those changes, that can lead to significant problems, too.

And I think that's the point I was trying to make with continuous improvement, is if the regulatory process is tedious, the methodologies that we use to define comparability or establish comparabilities are difficult. Then the technology, the innovation is hindered, and I think we have to start thinking more proactively in terms of how we move forward here.

And this is the point I want to make, is when you start bringing drug and drug delivery systems, you have not only a large number of factors to understand and optimize, but you have an even larger number of interaction terms, and these include, I think, considerations from anatomy, physiology and pathology, pharmacology of the drug, pharmamechanics of the drug, biopharaceutics, physical and chemical attributes of the drug, the polymer, and your device.

And in fact, the drug delivery system itself is quite complicated, and if we remain in

sort of a black box mode, bridging studies, post approval changes, even establishing specifications can be very challenging.

So I think we have to start thinking of more of an engineering approach to designing these systems, and that's the phrase I have used, is quality by design. We all know Quality 101. You cannot test quality in the product. I mean, that's well established. You have a design for quality.

And I think I have defined quality by design as achievement of product and process performance characteristics that are adequate for the intended use through scientific understanding and management of sources of variation and other risk factors due to manufacture.

Most of this process gets started in the development itself, and based on my experience at FDA, much of this information is not either shared with FDA or there's a strong hesitation to share this. So the regulatory assessment without some of this information can sometimes become quite challenging.

So I was recently looking at Los Alamos Laboratory presentations on designing missile systems and so forth, and I stole the plane from that slide, and I think the key here is what are the design objectives, the target to reach our target goal, and in the case of drug delivery systems, they have very exciting design objectives, and I think the hypotheses out there are mind boggling, and I think the innovation that will occur in the next ten years is going to be amazingly productive and useful for public health.

But I think we have to be very diligent in moving towards this in a structured, scientific way to make sure the innovation is not hindered because of regulatory concerns or, as one of the speakers used, fear of the unknown.

If I take a look at drug delivery systems now, past and present, our focus has been on changes in route of administration and bringing drug delivery systems through different routes. Clearly the deployment, how we administer this has been relatively simple.

For example, if you have a transdermal drug delivery system, some of the key features that are important for deployment is the adhesive performance, but the deployment can get more complicated, say, if you think about a drug eluting stent. It's a procedure that require additional deployment attributes to be considered.

Drug delivery in the current situation is primarily based on PK and PD, and the intention or the design objectivity of the drug delivery system is between proof compliance, patient compliant, and also to improve safety and efficacy. Many have used examples of the peak concentration and potentially that relating to safety, and I think more controlled release allows you in many ways to improve safety.

But the future, I think I see the deployment attributes could get more complicated because now you're looking at more sophisticated devices either implanted or otherwise, and you may have to have considerations for what are the right deployment attributes and how does a drug coating or

a drug combination alter that or how do we manage that from a chemical stability, shelf life perspective also?

And clearly I think the desire is to move towards more target oriented drug delivery system. The challenges and the opportunities associated with those challenges are currently in the pharmaceutical development quality and performance consistency has been based on traditional chemistry testing. I feel, and I think the previous presentation made a good point for that, that there are gaps in physical test. We have a difficult time addressing physical changes which are important and establishing shelf life based on physical changes are still more complicated.

The way forward in my opinion is we have to be proactive and look for these challenges and start working on those now. If we don't then we create bottlenecks and its difficult to get over those bottlenecks.

Clearly, if I just use a quick example of drug coated stent, but starting with stents

themselves, I think if you look at what are the design considerations here, intracoronary stents are deployed to form a scaffolding for the coronary artery vessel wall during coronary angioplasty. So I think the applied and the procedure leads to a number of issues that I think we have to think about.

How does the drug coating affect this process? Or is this process affecting the drug coating itself, and so forth? That sort of comes through that in the design consideration.

I'm going to skip this slide.

So as we start thinking about how do we identify and optimize critical factors, trial and error experimentation under all selected conditions is one way, but I don't think it's practical. There are significant opportunities where I think quality by design brings in an engineering approach where computer analysis employs numerical techniques of finite elements coupled with completion of fluid dynamics can help us understand our systems better and actually help us control or design systems that

will address the sources of variation quickly and up front and also have this information available to at least discuss with the agency.

One of the issues, i think, which is quite important, is the release rate. Many speakers have essentially argued the importance of the release rate from either drug eluting stent or any other delivery system. But what are the design objectives? What is optimal in vivo release profile? What is the mechanism and rate and duration of this release? How do we establish specifications?

These are important questions, and unless we think of different ways, the way today is to establish these specifications based on a limited amount of information. The opportunity is there to actually get to the mechanisms of these release profiles and actually start building back into the decision making criteria both in the companies and FDA.

So how do we establish controls and tests? Factors that influence release profile in vivo as well as design feature itself and

manufacturing factors, in vitro test methods, quality assurance, and in vivo relevance I think are important questions.

And with a focus on testing to document quality, these would be quite challenging, but with a move towards quality by design through scientific understanding, I think we can find a better way of moving forward.

For example, I think with drug eluting stents what is an appropriate in vitro method? I think that is a significant discussion point and a debating point of how does one start addressing that question.

Is that the right way of dealing with the quality issues or even establishing in vivo, in vitro, and real correlation? I think these are topics that I think we need further discussion.

The only point I want to make here is if we assume traditional drug release profiles and use, for example, bulk elution models, this is a publication from MIT-Harvard. Professor Hwang is one of the authors of this, and this was published

in Circulation, essentially identifying some of the challenges in terms of drug release.

If you use traditional approaches, we get a flat concentration profile, but if we examine the coronary artery after application of a stent, there's a potential for localize effect, which may be very different from and is not picked up by the traditional pharmacokinetics modeling.

So if we establish an in vitro release profile or an in vivo release relevant to a traditional in vitro/in vivo correlation, is that the right question? Is that the right thing or are we even asking the right question?

So these issues come up. So I think there is a wonderful connection between the new initiative and the initiative on drug quality system, and I want to sort of end my presentation - I'm on time -- end my presentation with a couple of slides sort of explaining the other initiative and so that you can see the connection between the two

In the direct quality system for the 21st Century, I think what we have articulated here

is a vision. Pharmaceutical manufacturing is evolving from an art form to one that is now science and engineering based. Effectively using this knowledge in regulatory decisions as we establish specifications and evaluating manufacturing processes which can substantially improve the efficiency of both manufacturing and I would argue development manufacturing and the regulatory process.

This initiative is designed to do just that through an integrated systems of product quality regulation founded on sound science and engineering principles for assessing and mitigating risk of poor product and process quality in the context of intended user of pharmaceutical products

So the desired state essentially as we have defined here is product quality and performance achieved and assured by design of effective and efficient manufacturing processes, and this is the point I was making. Product specification based on mechanistic understanding of how formulation process factors impact product performance, guarantees real

time assurance of quality, but in order to get there, I think the regulatory system that has to evolve, our regulatory policy should be tailored to recognize the level of scientific knowledge, supporting product applications, process validation, and process capability.

Risk based regulatory scrutiny then relates to level of scientific understanding of how formulation and manufacturing process factors affect product quality and performance, and the capability of process control strategy is to prevent or mitigate risk of producing a poor quality product.

With that I'll stop. I know we're running late. If you have any questions, I think why don't we have you sort of contact the speakers directly?

So we will hold the questions to individual questions if you can catch us. If not, then have a great lunch. Thank you.

(Whereupon, at 12:49 p.m., the meeting was recessed for lunch, to reconvene at 2:00 p.m., the same day.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(1:47 p.m.)

DR. PROVOST: We did offer the public the opportunity to comment, and we did have one request to speak, and that is Dr. Paul Goldfarb. He's with Oncology Associates and is a clinical professor of medicine at U.C.-San Diego, and Dr. Goldfarb will make his presentation now.

DR. GOLDFARB: Thank you.

My name is Paul Goldfarb. I'm a surgeon actually, and I do cancer surgery. I trained at Memorial Sloan-Kettering, and so I guess in the context of today's meeting I'm a maximally invasive radiologist.

(Laughter.)

DR. GOLDFARB: I have had the opportunity to work with two different companies that deal with ablation of tumors using drugs. I find it intriguing because in doing surgical oncology we're always looking, despite what most other physicians think, we're actually looking for new ways of achieving the same goals using less

invasive technologies and trying to find new ways of dealing with it.

I've been to the agency several times with Genetronics, and I've certainly been aware of the work at FeRx and have helped them do one of their trials that we'll discuss today as well, and the reason that I've come again is because I think these are critically important issues to us who do clinical medicine and surgery that need to be addressed.

Today I'm using a computer generated presentation. The last time I came in November I did it with overheads. So even I have moved forward with the technology.

I think there's a pressing clinical need to develop new technologies to control localized disease. I think more and more we're finding other needs to control local manifestations of disease, either primary or recurrent.

We're looking for less invasive ways of doing it, and we want to find ways that are more protective of normal tissues. The rapid adoption of

thermal ablation targeted radionucleotides, hypothermia, embolic agents, and cryosurgery reflects the fact that all of us are looking for these noninterventional ways of approaching these kinds of tumors.

The drug-device combinations as novel drug delivery systems provide the potential to enhance the effectiveness and reduce the adverse events of intertumoral delivery. Right now we have tumor ablation systems that combine drug delivery systems in multiple parts of the body, and as you can see from the slide, those are all of the organs, all of the solid organs that we're now looking at using drug delivery systems to try to treat with local therapy.

Now, we are able to achieve high local drug concentrations. There's low systemic exposure, and we have equivalent response in the tumors to other ablative forms of therapy, including surgery, the advantage being that we're able to preserve adjacent normal tissue.

This is one of the ways I actually got

into doing radio frequency, was that it seemed like such an obvious move that if I could use an ablative technology that would preserve the half of the liver that the tumor was sitting in, that I'd be able to manage the patient much better than doing right hepatic lobectomies, even though it pays less.

The two companies that we want to talk about are FeRx. FeRx you've already heard described briefly this morning in the discussion by the radiologists. It's an intertumoral drug delivery system which takes doxorubicin and uses small magnetic pellets to put the drug directly into the tumor.

And as you saw this morning, it's easy to target the tumor using the technology, using a simple external magnet.

Genetronics is a company that uses electroporation as its way of enhancing the delivery of drug. Electroporation is the technique where you create an electric field within the tumor by using a series of needles. You inject the bleomycin into the tumor initially, and then by creating the field

you allow the drug to enter the cell, and you essentially get ablation of the malignant tissue with protection of the normal healthy tissue around it.

In both of these systems -- and that's why I came back, because now we really have two different products that address things the same way. Utilizing well characterized drugs with known safety profiles, we deliver the drug to a localized area with minimal systemic exposure.

What we're really doing is utilizing novel devices to deliver this well established drug. In both systems we have an ablative effect that's confined to the area of the drug delivery and affects malignant tissues independent of histology and demonstrates a clinical benefit analogous to that of thermal ablation or surgical resection.

The issues that I want to talk to you about for a few minutes are the regulatory pathways and the standards that we're using for these sorts of products I believe are inappropriate for the perceived clinical benefit; that in both cases CDER

is the lead review agency for both of these combination products, and I understand why CDER is the review agency, and my education in this that has gone on for the last five years has taught me that the issue is really not which agency reviews it or which division reviews it, but how it's reviewed, and so I don't think that's an issue.

There are no other products that have localized ablative effects at disease sites that have been required to do such extensive testing and have such extensive review.

The drug components of these combination products in both cases that have been approved and used clinically for decades, they have safety profiles that are well characterized. They have extensive scientific and medical therapy supporting multiple therapeutic applications, and the technologies in these two cases are being developed by using reduced therapeutic doses of drugs.

So really the dose of Adriamycin or bleomycin used in these technologies is essentially homeopathic, and that they have minimal systemic

exposure to the drug. Both of these products which have a local effect are currently held to the same evidentiary standards and regulatory burdens of new drugs having untested and potentially significant systemic effects.

FeRx is in the process of conducting a Phase III study of over 200 patients with hepatocellular carcinoma, comparing their local therapy to a systemic chemotherapy in patients with end stage disease, and the study is using the survival endpoint.

The Phase I and II studies have already been done, demonstrated efficient tumor targeting using their product with Adriamycin; showed durable local disease control; and showed that the dosing paradigm was really based on the size of the tumor and not on the patient weight.

The new paradigm that we're looking at is to use ablation therapies regardless of what they are in terms of hepatocellular cancer because we now use it as a bridge to liver transplant. Liver transplant is perceived as the gold standard for the

treatment for liver cancer. The role of ablation technologies has really become one to stabilize the patient until the liver is available.

And so in a sense, that's the clinical arm. That's where we would be using it clinically. We'd be much less likely to use this local ablation therapy in people with far advanced disease.

And as I say, stabilization of the disease then becomes a viable surrogate clinical endpoint because that's what we would be doing in a clinical environment.

Here's an example of how the FeRx product works. Here's a tumor. You see the blood supply on the left.

Since I took my pointer back, I'll have to use -- there's the tumor, and you're able to actually put the drug just where the tumor is and have the clinical effect of ablating that tumor.

What's been interesting and what I've worked with FeRx on is using the same technology in a group of patients who have metastatic cancer. So these are people who have non-hepatomas, and the

question would be: can this drug Adriamycin, which we normally would not use in these other settings, be of value?

And, two, the thought had always been that the blood supply to metastatic tumors was such that it didn't allow for easy interarterial therapy. In fact, what we demonstrate, and these are studies using PET scans, and so what you're really saying is that this is the tumor before treatment, and the patient after treatment. At least physiologically you can say that the tumor is not viable.

These are early studies, but we certainly plan on following up on this, and I think this is the future for this kind of therapy. I use it to highlight the issue that the therapy works independent of histology just as radio frequency works independent of histology.

This was the second patient where, again, there's the tumor and there was the effect on PET scan.

Genetronics is a company that has a local therapy, and they embarked upon treating head

and neck cancer as the model that they wanted to test in, and we were initially involved in a classic Phase III randomized trial in which we were going to take people with far advanced head and neck cancer. Half would get this local therapy. All would get systemic chemotherapy, and we would try to demonstrate a survival advantage.

I must say as a surgical oncologist I thought that the study was inappropriate in the sense that that's not where I would use a local ablation therapy, and I thought the chance of meeting that goal was unlikely to occur.

And so I called Mark Kramer about a week after he got his new job and said, "You're in Combination Products. I've got a combination product. We need to figure out where do we go from here."

And so with Mark's help and in renegotiating with CDER, we have now evolved a study which I think is more clinically relevant in which we take people with early recurrence or second primaries, and we're looking at comparing the role

of this ablation technology to surgery because that's really the standard.

I would not expect that the ablation to do better. So as we saw this morning when they were talking about stents, we're sort of trapped because we have this positive gold standard comparator rather than comparing it to nothing.

But I think what we could show is that the control rate of these tumors will be no worse than it is with surgery, and arguably since we're able to do a much smaller, less invasive procedure than what I would normally do as a surgical oncologist, we should show functional improvement, and we should show pharmacoeconomic advantages that it should be cheaper and easier to achieve the same goals.

Now, the ongoing challenge is this is a stretch for the people at CDER just as it's a stretch for all of us, and so it has required ongoing negotiations about what really is a functional benefit and how do we measure this and how will we really know what's going to happen.

What we had shown originally with electroporation is -- I'll go over it. At the agency's behest, we took a bunch of people and injected bleomycin into the tumor with no electroporation, and we got essentially no result.

We then took people with far advanced cancer and injected bleomycin, electroporated them, and essentially we got a 50 percent objective response rate.

But we also had a group of people in Europe who had primary head and neck cancer, and these people were treated in a way that's very similar to what's been done with ablation. They had their tumors electroporated, which consists of injecting drug, putting the needles in, treating the whole tumor. They were electroporated, and then several weeks later the tumors were cut out. So we basically had a treat and resect model, which is the classic ablation technology.

In those now 20 patients there's nobody who has had a local recurrence out to two years. There were three who had microscopic cells in the

resected specimen.

I argue that if I was coming with a new form of ablation technology that used luke warm temperature instead of hot or cold and I said we have 20 people where we treated and resected, we'd have a discussion about whether this is approvable instead of embarking upon a 400-patient study.

I realize the challenge that I'm presenting, but I think that these are issues that need to be raised, and since the afternoon is set aside for discussion of regulatory issues, I hope this is a good lead-in to that discussion.

Now, my suggestions are both of these products are subject to review standards typically applied to novel drugs with unknown risk and safety profiles, with large numbers of patients, and a survival endpoint. The device products that have been approved for local ablation type effects have been subjected to much less extensive clinical data requirements.

Given that the safety profiles of both drugs are well characterized, there's minimal

systemic exposure. The requirements for approval should be comparable to devices that have an ablation effect.

When I came in November, my approach was basically at that meeting that we should look at all of the -- everything we're dealing with either has a local effect, a regional effect, or a systemic effect, and so it doesn't matter, I would argue whether it's a drug, a device or a biologic. We look at the effect on the patient, and that sort of defines how we should look at it in terms of regulation, and that might make it easier.

Both products are innovative device-drug combinations that utilize a new route of administration for old drugs, drugs that have been formerly administered intravenously and should have reduced time in clinical development and reduced evidentiary requirements.

Recommendations. New therapies need to be compared to other therapies that have a similar effect on the patient. Therapies which are local, regional and systemic in their effect should be

compared to therapies with a like effect regardless of which division is assigned as the lead, Device Drugs or Biologics.

To expedite the review and approval of innovative devices for the delivery of known drugs, the evidentiary standards must be appropriate to the potential risk-benefit in cancer patients. And I speak basically as a surgical oncologist.

We need to implement new regulatory pathways and least burdensome principles for innovative technologies that allow for rapid market entry and for patient benefit.

I've been working with these products for over five years. It seems to me that after five years and several hundred patients were treated it would be nice if we could find a way to move this forward in a more expeditious manner.

I understand what the barriers are, and certainly we're living within those guidelines and moving forward, but I think as a surgical oncologist, first because of my surgical personality, and then, two, because of my ongoing

clinical needs, I come to say to you we need to find a better way to do it.

I'd close by saying it reminds me of what Yogi Berra said. Yogi Berra said that in baseball 50 percent of baseball is 90 percent mental.

(Laughter.)

DR. GOLDFARB: And so I think regulatory approval is the same in a sense in that regulatory approval, 50 percent of regulatory approval is 90 percent negotiation, and so I hope that this opens the door so that we can continue that process.

Thank you very much for allowing me the time.

(Applause.)

DR. PROVOST: Thank you.

And now I'd like to introduce the moderator for the first session of this afternoon on regulatory issues, the industry perspective, and we're very pleased to have Dr. Liz Jacobsen here. Liz is a former FDAer, was at FDA for a long time, and is now at AdvaMed as the Executive Vice

President for Technology and Regulatory Affairs.

DR. JACOBSEN: Well, thank you very much, and it always bothers me a little when they say "a long time."

(Laughter.)

DR. JACOBSEN: Welcome to the industry perspective session. It's my pleasure to be the moderator for this segment and also for the final session, which is going to be the FDA-industry kind of Q&A session.

And we're hoping to get some good discussion going at the end of the day, and first we're going to have remarks from sort of a legal perspective from the device and drug industries and from FDA.

So we are going to ask you if you would hold your questions for those sessions, either hold them in your head so you can go up to the microphone at the last session of the day or write them down and you can give them to Miriam at the break or whenever you see her, and she'll make sure that they get up here, and we're hoping that that will work

because obviously we would like to have some good Q&A.

Okay. Well, first up in this session, the industry perspective, is Jonathan Kahan, partner at Hogan & Hartson, and he'll be talking about regulatory and legal challenges for the developers of drug delivery systems.

MR. KAHAN: Thank you very much.

Good afternoon. I want to thank Dr. Feigal and Dr. Provost for inviting me to speak this afternoon. I promise to be on my best behavior.

And there is good news and bad news, I think, in my presentation. I think the good news is I will have no slides of blood fields or tumors, and the bad news is I'm going to try to walk you through some fairly dry legal and regulatory issues, although I'm also going to try to give you, I think, the perspective, at least my perspective, on some of the significant issues that industry has faced over the years in this area.

I'm going to start out by talking very briefly about the legal framework. I'm then going

to talk about the historical approach that FDA has taken to the regulation of combination products and drug delivery devices over the years.

And then I'm going to talk about the obstacles and challenges that we're all facing in this area and try to talk about some new policies and procedures which may be appropriate in this area to try to change around what I think a lot of us, including many at FDA feel is not an optimal area right now. There are many, many delays and inefficiencies in the process, and I think we're going to have a good discussion about that this afternoon.

Just for those of you who are interested in definitions, a lot of what we're going to be talking about this afternoon has to do with the definitions of drugs, devices, and biologics. And without going into too much detail and putting everybody to sleep, basically drugs are articles intended to prevent, cure, and treat disease, intended to affect the structure and function of the human body. It's basically the same definitions for

devices, except the devices do not typically achieve their primary purposes through chemical or metabolic action.

I'd say the rule of thumb is if it's more mechanical, it's a device. If it's more metabolic and chemical, it's a drug, although they, as we'll talk about probably in depth this afternoon, they very often tend to merge, and it becomes a very metaphysical discussion as to whether the action of the product is chemical, metabolic, or physical. In many cases, as we'll discuss, it's all three.

Biologics, I have no clue as to what a biologic is.

(Laughter.)

MR. KAHAN: This is the definition of biologic. It's sort of like pornography. You know it when you see it, but it's hard to define, and biologics are basically derived -- there are definitions under the Public Health Services Act and we'll talk about in a minute that are actually products that are combinations of drugs, devices,

and biologics, all in one specific product.

Just historically, just to give you the perspective of what we've all been facing for years and years, back before 1990, we sort of addressed all combination products, including drug delivery devices on sort of a case-by-case basis, and you've heard that very often it was a question of negotiation, and that's absolutely true.

In many of these cases, there was negotiation not only between the companies and FDA as to how the product was going to be regulated, but there were also negotiations within FDA as to how the product was going to be regulated.

I'll give you just one example. I'm going to try to keep the war stories to a bare minimum, but biliary lithotripters is just a good example to start out on and combination products generally because with respect to that product you had a lithotripter that could fragment gallstones, but it needed to be used with a litholitic agent, which at that time was ursodiol or Actigol, the product that was on the market at that time.

And the companies came to FDA and said, "We want PMAs for our lithotripters. Clear these devices."

And FDA said, "No, this is a combination product, and it needs to be used with the drug," and they said, "But the drug has already been approved for the dissolution of the stones."

And Steven Fred then in Gastro at CDR came back and said, "Wait a minute. It was cleared for nonfragmented gallstones. We need an NDA supplement for fragmented stones."

That was basically the end of the process. The drug company was not willing to work with the device companies, and 12 years later, probably 13 years later, the drug company finally decided to allow access to its NDA files, and that product was approved.

But that roadblock, which I'll talk about again in a minute between access to drug files and master files and IND files is one of the key factors that has led to many, many problems over the years in the drug delivery area and in combination

products generally.

How did we seek to resolve this issue? I believe that the disaster we face on biliary lithotripters was one of the reasons that Congress decided to address the law in the Safe Medical Devices Act of 1990, which added the combination product regulations.

As a matter of fact, the person who actually drafted the first combination product statutory division was Pat Schraeder, who's not here today, when she was working with Senator Kennedy's committee on that, and at that time, the first draft of this regulation and statute was essentially designed to allow one filing. There was not going to be an NDA and a PMA for one product.

Congress backed down on that probably through the second or third draft of the law, but essentially what came out of the law was we need some structure to combination products, and the way we're going to add structure is we're going to work with FDA and we're going to say that the primary mode of action is going to be the key standard for

determining whether a product is going to be regulated by the device center, by the drug center, or the biologics center and under which statutory authorities is that product going to be regulated.

The problem is that Congress never defined primary mode of action, and to this day it has never been defined, and FDA, as I understand it and will talk about this this afternoon probably during Mark Kramer's presentation, FDA, I believe, is now starting down the road of seeking to actually define primary mode of action, and I think we all welcome that.

Mark is also going to talk about the definition of combination products. So I'm not going to get into it very much, but simply to say that the technologies that are coming along right now are mind boggling. You've only heard of some of them, and I never cease to be amazed by the combinations of drugs, devices and biologics that are presently on the drawing board and which FDA is going to be facing very shortly.

And one of the things that we're going

to talk about today is whether the 20th Century standards and regulations that FDA now has in place are going to be adequate to handle the 21st Century technologies that are presently coming down the pike. It's no longer going to be are we looking at prefilled syringes, but are we going to be looking at products, for example, a dopaminergic cell that's encapsulated in a semi-permeable polymer that elutes dopamine. So you have a drug, dopamine. You have a dopaminergic cell, which is a biologic, and you have a semi-permeable polymer, which is a device. And there are many, many products that are presently coming down the road that are going to be combinations of many different kinds of tissues, drugs, deices, and biologics.

So I'm going to let Mark handle the rest of that one.

(Laughter.)

MR. KAHAN: With respect to exactly the regulatory structure, again, others are going to be better able to deal with this. I'm just going to very quickly talk about sort of what really happens

when a company has a combination product.

Over the years, we basically have dealt initially with the product jurisdiction officers. That would be Warren Rumble right now in drugs, Gene Burke over in Devices, and Cheryl Lord Weiford over in Biologics, and often we simply seek to get an indication or a feeling from them when we initially have a product.

What do you guys think, based upon your institutional memories? Do we need to file a request for designation?

And under the Safe Medical Devices Act of 1990, Congress said, "Wait a minute," and FDA implemented regulations under Part 3 that said, okay, if you're not sure, you can file an RFD, a request for designation, and we will tell you within 60 days how we're going to regulate your product, what's the primary mode of action, and in some cases in those letters, they actually tell you whether it's going to be a PMA, a 510(k), and what the NDA process may look like.

And we often start out with discussing

these issues with the product jurisdiction officers. We find that helpful. We then move on to the request for designation, and the next stage is, once you've gotten the designation, we then go to a pre-IDE or a pre-IND meeting to actually flesh out exactly what the data requirements are going to be.

Now, if you're a smart company, you start thinking about the data requirements at the early developmental stages of your product, not when you're sitting down with FDA and talking to them in a pre-IDE or a pre-IND meeting.

And, therefore, I think the most important thing I can probably say today is start early and communicate very well with both your clinicians, your engineers, your regulatory affairs people, and try to prophesy early on what you might need for that pre-IDE, pre-IND meeting later on.

And then you're going to later have to face, if it is a combination product, coordination between CDRH, CBER and CDER. Mark will talk probably more about exactly what they call their consultative meetings and their collaborative

reviews and consultative reviews.

But the bottom line is if it's going to be one center with primary jurisdiction, they will consult with another center, and if it is a collaborative review with two primary reviewers, you're going to have input from two centers at once, and that's often not the best way to do it.

So I think most of us would try to seek to have one center with primary jurisdiction and the other center consulting so that you're not whipsawed between two centers during the process.

Just to again give you the historical picture here, over the years FDA has sort of developed their own gestalt internally, some of which is reflected in the inter-center agreements, which I would urge all of you to read, although I'm about to tell you I think they are out of date, outmoded and need to be revised.

But they give you a picture of what FDA's thinking actually is, and if you look at the inter-center agreements, you'll see that things like prefilled syringes and infusion pumps and

transdermal patches, those kinds of things have all been pretty much defined as to how FDA is going to look at them. That's what I call the early generation products, although ionaphoresis devices have given FDA heartburn for quite some time, and I won't go into how FDA has regulated ionaphoresis devices over the years, but it's not a pretty picture.

And with the new products coming down the road with regard to ionaphoresis devices, hopefully meetings like this can help develop new paradigms for how to regulate products like that.

Simply another very quick example on metered dose inhalers, if those of you who remember those products were originally all regulated in the device center through the 510(k) process, there were then I wouldn't say it was a fight. It was a very cordial discussion between the device center and the drug center about whether the droplets and the size of the droplets and the efficacy of the drug that is taken in through the metered dose inhaler requires the inhaler to be regulated in the drug process with

the approval of the drug, like albuterol sulfate, for example.

And that's what happened. All got shifted over to the drug center based upon the safety and efficacy issues that CDER thought were raised as part of the drug delivery process of the drug.

The second generation products, most of you didn't realize that your cigarette was a drug delivery device. Neither did the Supreme Court, and --

(Laughter.)

MR. KAHAN: -- therefore, that issue is no longer on the table, but there are many other products during the second round, which I believe FDA has been thinking quite a bit about. The drug-coated catheters and stents have primarily been regulated through the device center where the drug coating on a catheter, for example, if you had an antimicrobial catheter, if it's an approved antimicrobial the device center has pretty much kept jurisdiction.

On the drug-coated stent, you've heard a lot about that. We're going to talk a lot more about it later. The bottom line is there that I believe that what FDA did there they should be congratulated on. It was a very well thought out, a very common-sensical approach. The studies and the way FDA is handling that I think is optimal, and I hope that that kind of paradigm can be used further in the future.

I did sit in in one meeting where Dr. Lipicky, the head of Cardiovascular Drugs, indicated that he wanted a 10,000 patient study, and I think the device company fell out of their chair at that point, but what we ended up with was studies that started out initially with 1,000 patients, with post-market requirements up to a couple of thousand more patients.

And while it is true that a two to 3,000 patient study cannot meet the ICH guidelines for a one in 10,000 adverse event rate, identification rate, I believe that the approach that's been taken here with the coordination between the drug center

and the device center and the working groups that have been set up is absolutely a paradigm that can be applied to other drug delivery devices in the future.

I'll just mention a couple of others. There are drug delivery lollipops. In working on that one, FDA's primary concern was that Grandpa would leave his fentanyl lollipop on the stand and his grandson would get a nice dose of a controlled substance, but chewing gums and lollipops and other drug delivery devices through the oral mucosa is another way that we're going to see in the second generation those are already now on the market and in use.

Now, this third generation of products is one that I think is going to cause FDA a lot of trouble, and it's going to cause the companies a lot of trouble, and it's going to require a lot of creative thinking, and we're going to talk about this in a second, but one of the major issues that we're going to be facing now is that some of these drug delivery devices are going to be delivering

multiple drugs at one time.

And let's say that you had -- I think Dr. Langer talked about the microchips device which could have 100 wells, and let's say you're going to have 20 different drugs in those 100 wells. Do we need to get an NDA supplement or an NDA for each drug that's going to be in that little pacemaker?

I think those are the kinds of issues that we're going to be facing in the very immediate future.

I'm now going to talk about the challenges that we're facing with these products, and I'll try to be quick because I don't want to take too much more time.

Drug delivery devices are often developed initially by the drug companies for uses with approved drugs or biologics, and that usually is the easiest paradigm to deal with. If it's an approved drug, usually CDER and CDRH are pretty comfortable with it, and that's why you will see some of the silver-coated wound dressings or antimicrobial bone cements. There's not too much

heartburn at FDA about that, and the agency has been able to regulate those products fairly well.

However, when you switch to new or different indications for the drug or you have a different mode of delivery or a different drug or dosage schedule, all hell breaks loose, and then you have to really start in what is essentially a scientific regulatory negotiating process with the agency.

And the question then is when you modify the drug formulation to optimize delivery with the device, are you now having, as a couple of people have said, are you now about to reinvent the wheel and have to start over with, let's say you can skip Phase I of the drug process and go to a Phase II/Phase III drug trial, at the same time that you're demonstrating the safety and efficacy of your device.

That is not something that most device companies want to do. They do not want to reinvent the drug wheel. And so the question is: is a new NDA required for the drug if you have a different

delivery mechanism than the mechanism that was described in the NDA-approved label?

In other words, the NDA was approved for IV use or subcutaneous injection and now you want to deliver it in that little pacemaker that's implanted. Does that require you to have to go through an entirely new NDA process?

Let's say that you change nothing with respect to the drug that's being delivered, although there may be stability issues and a tiny bit of a reformulation. Are you going to have to start the NDA process over again?

I'm going to raise a lot of questions. I'm not even going to pretend I have the answers to all of these questions. I tell my kids I have all the answers. They don't believe me either, but I'm not going to try to answer all of these. Maybe this afternoon with people smarter than I we'll be able to try to answer some of these questions.

All I can say is that it is not optimal to start over when you have a new drug delivery device, to start over in the entire new NDA process,

and I'll talk about a couple of alternatives in a second.

So the question is, when you have this sort of combination of a drug delivery device and either a new drug or a drug which has been modified, which predominates in the review process? Is it the PMA for that new novel MicroCHIPS pacemaker type device or is the NDA process going to predominate?

And does the device labeling have to conform, mutually conform to the drug labeling? This is an issue which Mark has on his plate right now for several different companies and the inter-center agreements say that the drug labeling and the device labeling have to mutually conform.

So you couldn't clear a device, theoretically, unless the device's labeling was in conformance with the drug labeling, and the inter-center agreement primarily talks about conforming in terms of formulations, dosage and schedule, but it doesn't necessarily address all of the issues.

For example, if you have a device that's now being delivered subcutaneously and you now want

to have it implanted in a pacemaker to deliver the drug over time, does that now mean that you have to have an NDA supplement or change the drug labeling?

And if you're not the drug company, what do you do? You can't change that drug company's labeling if you're a device manufacturer. So what do we do?

Here's the challenge. The challenge is that if the pharmaceutical manufacturer authorizes access to their master files, their DMFs or they authorize access to their NDAs and their INDs, all of the world would be a lot easier, and it is not very often that you have the drug and the device company in the same shop. I mean, there are companies like Johnson & Johnson and others that are lucky enough to have both drugs and devices in the same company, but very often the device company doesn't have access to the drug company's files.

So especially if the device allows a broadened use of the drug the pharmaceutical company would probably likely agree. That's more drug sales and, therefore, they're more likely to grant access

or authorize access to their master files or their NDAs.

But in some cases drug delivery devices allow a more optimal and efficient delivery of the drug, and therefore, less drug is going to be sold if that drug delivery device is approved by FDA, and that's a disincentive for PhRMA to cooperate with the device industry.

So what are the regulatory implications here? Without PhRMA cooperation the device companies have a very difficult time obtaining NDA approval, as we saw with the example I used earlier with respect to Actigol and the biliary lipotripsy paradigm.

The applicability of Section 505(b)(2) is an issue presently on the table. 505(b)(2), it's not really a paper NDA, but it's like a paper NDA where you rely upon literature and existing data to avoid having to file a 505(b)(1) brand new and spanking new NDA.

And query whether a device company using the 505(b)(2) process can with a different, let's

say, route of administration and a clear drug product, can they then rely on 505(b)(2) without a drug manufacturer even on the horizon to get their product through?

A real tough issue. I don't have the answer. It is something that a lot of companies are looking at, and it is one way for the companies to proceed.

The regulatory pathway conundrum: should a 510(k) or PMA be required with an NDA for each new drug delivery device? In the QLT example with photodynamic therapy we had sort of a pullout PMA for the lasers and the fiber optics that went in at the same time as the drug NDA, and believe it or not, it was a miracle. The three PMAs and the NDA were all approved on the same day.

That example worked out well there. There have been other examples. There was actually a 510(k) with a pullout NDA for these H. pylori breath detection devices where you had C-13 labeled "urea" having to be approved by the device center. That pullout didn't work real well.

So I think what I'm pushing for is more along the lines of what the FDA has done with drug eluting stents. If you look at the Cypher labeling, it looks like drug labeling through a lot of the package insert, and I believe that with these combination products, you can mix drug labeling with device labeling to appropriately reflect the intended use of the device with the appropriate precautions and warnings such that the user of the product will have information that's appropriate for both the drug and the device side.

The lead center conundrum, I'm going to let Mark address this since I'm just about out of time, but let me just say that we need a new definition of primary mode of action. Primary mode of action is one of those areas where we need guidance from FDA.

There is a very, very extensive database of primary mode of action decisions under the RFD process that have never been made public, and in fact, I don't think FDA ever put them in one spot. I think Mark is now gathering the historical

precedents in this area, but I think we would all feel very much more comfortable if we entered into the process knowing more about what primary mode of action means.

Finally, just to sort of sum up here, I believe that there should always be a preference for one submission. The idea that you have to go through the NDA process and the PMA process or 510(k) process at the same time to me is not optimal.

And the idea that we had back in 1990 for a unitary approval mechanism, I don't know whether you want to call it a CPA or a combination product approval, but maybe we need new legislation that would allow us to look at whether we still want to keep primary mode of action as the standard.

Do we want to have a new statutory provision that would replace primary mode of action and go to a uniform, a unitary combination product approval to avoid what was just stated in the last presentation, where you end up with a disconnect between the way the drug center would treat the

product and the way the device center would treat the product?

And I believe that many in industry believe that there is a different approach to product approvals within the device center and the drug center.

Conclusions. Dual approvals, not optimal. I think most people would agree with that. Primary mode of action, standard. We need a new guidance. We think it's outdated.

I believe that guidance documents with respect to specific classes of drug delivery devices would be very, very helpful.

How about guidances with respect to drug eluting stents? What do you expect on the drug side? What do you expect on the device side?

Nasal inhalation devices, what do you expect on the drug side? What do you expect on the device side?

A lot of work. It's going to require a lot of coordination between the centers, but specific product area guidances would be very, very

helpful to the companies going through the process.

A uniform, unitary drug delivery device mechanism, such as a combination product approval, that would be great. More involvement by the Office of Combination Products. I'm not trying to get more staff for Mark, but I believe that it would be extremely helpful for the really novel drug delivery devices and combination products for somebody in the Office of Combination Products to have liaison responsibility with the centers, not that they need adult supervision. It's just it would be helpful to have some liaison and someone that's involved in the process from the very beginning to help negotiate and have a liaison between the centers.

Thank you very much.

(Applause.)

DR. JACOBSEN: Thank you very much, Jonathan.

Jon mentioned in his talk about Pat Schraeder being an early player in combination products, and Pat sends her apologies to everyone. She intended to be here to represent AdvaMed and to

give the device industry's perspective, but she had to cancel at the last minute, and we're very fortunate to have her colleague, Keith Smith, who is Director of Regulatory Affairs from BD who has graciously agreed to present this perspective in Pat's place.

And then Nancy Isaac, Vice President for Regulatory Affairs and Quality at Aerogen, is going to take her place later today on the FDA industry panel.

So with that, we'll turn it over to Keith.

MR. SMITH: Thanks.

Good afternoon. I'm sure most of you know Pat. So I certainly don't look like Pat or talk like Pat, but I'm going to do my best.

Okay. My name is Keith Smith. I'm Director, Regulatory Affairs at Beck and Dickinson, but I am here today as a member spokesman on behalf of AdvaMed or Advanced Medical Technological Association.

AdvaMed is the largest medical

technology association in the world, representing more than 1,100 innovators and manufacturers of medical devices.

One of AdvaMed's principal roles is to support laws and policies that foster innovation and bring safe and effective technologies, including novel delivery systems, expeditiously to the market.

In January, the FDA announced a new initiative to help make certain innovative medical technologies available sooner and to reduce the cost of developing safe and effective medical products. While still maintaining FDA's traditional high standards of consumer protection, we applaud the agency for identifying as one of the core areas of attention of this initiative novel drug delivery systems.

Novel delivery systems are an important subset of combination technologies ranging from implantable infusion pumps to magnetically based delivery devices, to systems that automatically deliver anesthesia drugs in response to a patient's vital signs.

The new technology intended to improve targeting of chemotherapeutics by blocking blood flow, novel delivery systems were identified as a priority area for FDA's initiative because they represent an exciting area of technology development with potential to significantly improve patient therapy and public health yet are often slow to reach market due to complexities and uncertainties in the pre-market review process.

Our discussion today focuses on these pre-market complexities and uncertainties and how we might improve our regulatory processes so as to further the Commissioner's goals of encouraging delivery system innovation.

The comments we provide summarize the principal concerns and recommendations received from AdvaMed member companies on the three questions identified in the June 5th Federal Register notice.

The first and most general and overarching of the agency's questions asked that we identify current critical challenges in developing and bringing to the market novel delivery devices.

As an initial comment, we are gratified that some of the historical challenges relating to regulatory processes are beginning to be addressed. As you know, AdvaMed, working closely with FDA and Congress, helped implement Section 204 of MDUFMA which, among other things, created for the first time in the Office of Combination Products having as one of its key functions to serve as an advocate for combination technology, including novel delivery systems.

MDUFMA also provided a statutory directive for the office to help ensure timely and efficient premarket process and to establish dispute resolution mechanisms should impediments arise during those processes.

With this new law, we have an important first step to refining and improving premarket systems in this area.

Challenges, however, remain; four in particular, all relating to the fundamental framework of premarket review, still requiring further consideration, clarification, and consensus