biologics controlled by diagnostics are going to be the future of diabetes therapy, at least, and perhaps in a whole bunch of hopefully other therapeutic regimes.

So how does the addition of a diagnostic tool change what we've talked a little bit about here today? So I have a drug that's made by one company, Christine's perhaps, and then we have a device, a pump, and then we have now a diagnostic device. Does that change anything in your thinking, your fundamental thinking about how these systems get approved?

And where I'm going is is the ultimate endgame therapy, delivery? Is there going to be the possibility of approval for a therapy that includes some of these kinds of systems?

DR. FEIGAL: I can give you an example of one that's already on the market that has got a diagnostic, and that's the variations of different pacemakers that sense rhythms, sometimes deliver intermittent shocking therapies, decide whether or not to pace the heart, and it does introduce a whole

additional number of issues in terms of the way the software is written. There's an amazing number of lines of code imbedded in the people's chest as they walk around, and you need to make sure that the software behaves properly in addition to the sensors behaving properly, in addition to the whole logic.

And then you have to prove that the whole strategy has a net benefit, and that I think has been one of the successful areas where the devices are actually starting to look better than the drugs that used to be used for arrhythmia.

So I think that's possible. I think that some of the challenges laid out this morning specifically for diabetes identifies, you know, that not all side effects are created equally; that hypoglycemia is potentially fatal and much more devastating than loose control. And so how do you back into this and how do you do this in ways? And it probably isn't even so much a matter of whether it's an implantable, tiny device, which we'd eventually like to see, or initially if it's something that's done in a more controlled

environment.

But I think that's where some of the paradigms are. I think what's interesting is you watch and you see these things being developed incrementally and you see changes, and this is different than drug development. You'll see a change in pacemaker features from the same manufacturer every six to nine months, and you'll see new strategies that are unproven being planned to be imbedded in the future models to treat different types of things. I imagine there will be that sort of incremental benefits in developing software for diabetes management. You may not try to do anything very complicated at first and deal with the safer sort of things that you can treat and then gradually work into the other things as you develop the safety track record for that.

What often you don't have is a sense yet of sort of what will the clinical and the patient population and the public bear in terms of complications. There are some products -- Jesse has unfortunately a couple of them -- where it's

national news if there's a single product failure. You know, one patient gets an HIV transfusion, and it's news.

And there's other products that are over the counter drugs that we tolerate a certain serious complication rate and even death rate, you know, a death rate from, and so how the technology is developed and the comfort that people have with the technology so that we don't make our patients into Luddites who think, "Oh, it must be the technology that is going to be bad."

How we build that trust as we build that to say that the products are safe and effective is very important, and it's a complex process. It even involves things like handling recalls responsibly and safety alerts responsibly.

There have been a lot of pacemaker safety alerts, recalls over the years that haven't undermined the confidence in the products because they've been viewed largely as proactive measures to deal with problems as they're discovered, as opposed to manufacturing problems that weren't anticipated

and other kinds of problems.

MR. KAHAN: Can I add just one regulatory point to that? What you're talking about in a regulatory sense is a closed-loop system where the actual control of the release of the drug is by a diagnostic feedback, and our discussions with FDA over the years on closed loop systems is that they certainly can be cleared through the agency. However, the approval process will be one that will be extremely rigorous because the potential for underdosing or overdosing if somehow there's a gap or a data glitch in the loop through a software or other problem has raised the agency's hurdles here.

And I think we've been talking about these products for at least ten to 15 years, and now they're about to come to be very, very quickly, and so can we think out of the box? I think the good news is that you're going to be, especially with insulin, you're going to be delivering a drug that has a well-known character and a well known profile.

On the other hand, the closed-loop side of this is going to lead to possibly FDA

scrutinizing the product more than they would scrutinize a pacemaker or an automatic implantable defibrillator because you're relying totally on the software and the feedback.

DR. JACOBSEN: Let's take this question, and then I have a written one that I want to ask.

MS. ITANI: Temima Itani with Ethicon Endo-Surgery.

I was struck this morning by the complexity of the programs that were presented, and I believe that they will undoubtedly present a big challenge to the regulatory system. I'm interested in hearing from the various center Directors here what are their thoughts on where FDA needs to go to meet these challenges.

What are the changes that need to be made, the competencies, et cetera?

DR. FEIGAL: Jon's taking the easy way out. We'll make you Deputy Center Director for the hour.

(Laughter.)

DR. FEIGAL: So that you can answer the

question, Jon.

But I think the hardest thing for CDRH, one of the things, we were talking about the culture differences. It isn't just the fact there's different application processes and things. The thing that is different and was alluded to a little bit in Ashley's slides is our responsibility to make risk-based determinations in an application.

And so even within an application not every question has to be settled with clinical data. So one of the hardest things is to decide which kind of things are actually better determined with performance specifications, engineering specifications.

And sometimes it's thought of as a lesser standard, but you know, I would argue there are some things like radiation therapy equipment where you'd rather have a physicist measure the beam than try and figure out how sharp the beam is by testing it on patients. You're better off with performance standards in that kind of setting once you've established that a beam has some therapeutic

uses.

So I think a lot of the strategies that were presented this morning, which included drugs which were activated by the use of energy, by the use of light, that included many new sort of novel fabrication technologies to make needles that were smaller than were possible before.

A lot of that, I think, comes down to really identifying what are the different characteristics of those products that are really going to be essential to their performance and that will make them safe and effective, and to figure out which of the things, even though they're new, are probably better determined by looking closely at the engineering than at the clinical data.

So I think that's probably going to be one of the challenges, is making that sort of risk based assessment. I think the fortunate thing for devices is that they are built incrementally and iteratively, change by change, and that gives us the ability to creep up on some of those technologies, but some of them seem awfully slow in the

development.

Was that in the 1840s that those laser -- that those light activated drugs started? That was a long time ago.

John, do you have any comments on new technology and how CDER can learn about it?

MR. JENKINS: Now that I've been promoted to head pointy head bureaucrat, I guess.

(Laughter.)

MR. JENKINS: I took offense to that remark.

I think the biggest challenge that we face in CDER is becoming more familiar and aware of the CDRH regulations and statutory provisions. Most of our reviewers really have very little knowledge about the CDRH process. So when they get asked to do a consult or a collaborative review for a drug device combination may be where CDRH is the lead center, it's really a whole new world for them.

I've watched the collaboration that's been going on for the last six or 12 months between Ashley Boam's group in CDRH and the Cardiorenal

Drugs Division in CDER, and I think they've developed a really good working relationship, a good understanding of the procedures, the regulatory hurdles, and the pathways, and I think that's worked very well.

So at some point you develop a critical mass of relationships and understanding that make it go well. All too often most of our divisions see one of these, you know, every year or once every two or three years. So you don't really develop that critical mass of knowledge.

One of the other things that struck me as I was thinking of answering this question is it may not be apparent to most of the people in the audience, but most of the people at CDER don't even know people at CDRH. We're not in the same physical location. We rarely run into each other in the cafeteria or whatever. In fact most of us don't even know where CDRH is located.

(Laughter.)

MR. JENKINS: So it would be, I think, really nice if, down the road, the White Oak campus

does actually bring us all together on the same campus where there can be shared training opportunities, where you can kind of walk across the courtyard and go to a device meeting rather than now trying to figure out how to get your way up 270 to go to a device meeting.

So I think training, opportunity to interact and experience go a long way to making these collaborations work well.

DR. GOODMAN: Well, you know, I think CBER has some unique perspectives on this that I think are relevant to this in terms of constantly dealing with a lot of new technologies and cutting edge technologies where risk is often uncertain, and where as David said, a risk based approach and an iterative approach is important.

I think these are big challenges for the agency. I think everything the agency does is a big challenge for it, but I think new technologies are particularly big challenges, and then new technologies that cross regulatory lines are even more difficult ones.

To me some of the things we need to strive for in FDA and you outside need to help us with are our expertise, you know, and when you're dealing with new technology, with new material science, with new biologics and cells or drugs, you really need people who are cutting edge and have stayed current.

So we need to invest in our own people in terms of being scientifically up to date, and I include there not just the technology, but in being in touch as much as possible with clinical reality, clinical trials, et cetera.

And I think most people at FDA would like to see that, but when people are working very hard and don't have a lot of time, that's one of the things that tends to suffer. It also suffers from the resource point of view, but I know all of the people sitting up here from the agency are very conscious of trying to support our people to be as expert as possible.

Anther part of that, I think, is collaboration and consultation both within the

agency and then outside, and how can we find nonconflicted ways, for instance, to collaborate more and get more outside the agency, and to me for CBER that's a real priority.

And finally, as I think both previous people said, I think, you know, this is sort of "Brave New World" technology that many of you have talked about earlier today, and it really has to be, as David said, in devices you see this all the time, but in the other areas we don't see it as much; that there needs to be this iterative approach to how we evaluate products and react to new information and a degree of flexibility that one needs to strive for.

But I think all of those things to do them, you know, have required expertise and good communication, all very resource-intensive stuff, but I think it's stuff ideally we want to work with you to do.

DR. JACOBSEN: I'm not a center Director. In fact, I don't even work for FDA anymore, but can I make a comment on this question anyway?

DR. GOODMAN: Sure.

DR. JACOBSEN: Even though it was asked for the center Directors.

Mark said earlier that he had really liked the talks this morning and this early afternoon, that he hadn't heard of a lot of the technologies, and that he thought that his take-away message as a result of seeing all of those exciting technologies was that companies need to dialogue with FDA. I think he said begin early, and I agree with that.

But I also would add that it seems to me that this kind of open meeting really helps that dialogue start to happen and maybe we should do more meetings with industry and FDA staff like this one where you really get a chance to hear the talks on new technologies like we heard this morning, maybe even have the products, you know, area specific.

I don't know, but sort of talking together about the technologies that are leading to these new and interesting combination products. I mean, the platform presentations were really

terrific, but the hallway conversations were just as terrific.

So that would be my suggestion, but I don't know how you all feel about that.

DR. GOODMAN: Yeah, we think it's great, and you know, the other thing some people have done is just come in and talk to us about their future plans and portfolios, and it's a little bit of, you know, meet and greet kind of thing.

On the other hand, we find it very informative to be aware of not just what's there, but what's coming to be sure we have the right kind of expertise.

DR. JACOBSEN: I have a couple of other written. I don't see anybody else at the mic.

The question is insulin is currently not FDA approved for IV route of administration. IV is an off label use. The insulin manufacturers don't seem interested in filing with FDA to do the studies for IV insulin to be approved, yet it's widely used.

If IV insulin was approved, then that would open the door for novel IV insulin devices to

be developed for hospital patients. Can IV insulin be cleared without much initiative from insulin manufacturers?

IV insulin devices are not approvable now with IV insulin being used off label.

MR. JENKINS: Sounds like a drug question.

(Laughter.)

DR. GOODMAN: We would be very open to having sponsors of the insulins come forward to develop, you know, approved indications for use of insulin IV. I think we already have the dosage forms. I think the forms that are available may be appropriate, although I'm not sure of that. There may be some modifications that need to be made in the preservatives or whatever.

Sometimes the agency finds itself in the situation where sponsors don't come forward, and sometimes we find that we have to develop the data ourselves. It may be possible that there's adequate data in published literature that someone could put together and come forward and submit a supplemental

application to get that approved.

Sometimes it comes down to we have to do it ourselves, which is obviously a very resource-intensive process to go through reviewing the literature and developing an understanding of whether the product is felt to be safe and effective, and then we can put out calls for applications.

So that's a question we could take back to our Metabolic and Endocrine Division, but I think we also have a representative from one of the major insulin manufacturers on the panel. So she might want to address coming to us for an indication.

MS. ALLISON: I think I'm probably not the proper person to answer that question, but it would still be welcome if anybody wants to discuss about this approach to our company, and we can talk about that.

DR. KLONOFF: David Klonoff from Mills Peninsula.

That was actually my question, and I just wanted to have a follow-up to that, which is:

do you think that if a device company came forward because they have a method of delivering insulin by an alternate route, namely, intravenously for hospital patients, that this would be sufficient for you to look into the IV insulin indication or would you still say that this device company must bring on board an insulin manufacturer?

MR. JENKINS: Well, I think there are different ways that you can approach it. Clearly the most straightforward way is as the question was written, is if the insulin manufacturers would get approval for an IV indication that would help, obviously, the device manufacturers.

The other approach would be for you to come in in partnership with an insulin manufacturer or maybe not even in partnership; just, you know, some of the pumps are not in partnership with the insulin manufacturers.

You yourself could be the one who could summarize the literature and try to present the evidence to support approval that, you know, IV insulin for whatever indication you're seeking is

safe and effective, and there maybe adequate data in the literature to help support much, if not all of that indication.

So I would encourage you to, you know, consider talking to the Metabolic and Endocrine Division about what they might need to feel comfortable for that indication.

DR. KLONOFF: Okay. Thank you.

DR. FEIGAL: There is one historical example. The very first H. pylori approvals were done based on literature reviewed by an FDA reviewer. It didn't occur to me at the time, but that might have had some user fee implications --

(Laughter.)

DR. FEIGAL: -- because if you were to come in with an efficacy supplement for insulin, wouldn't he need a drug user fee for that?

MR. JENKINS: Probably if you're submitting the simple clinical literature to try to support an indication. That would probably meet the definition of clinical data for review, but there obviously are also provisions for waivers of fees in

some cases.

We have taken the approach occasionally of, you know, developing the data ourselves. We did that with levothyroxine. We published a Federal Register notice saying that we, you know, based on the accumulated scientific evidence found levothyroxine to be safe and effective, and what we needed were manufacturers to submit NDAs to show that they could manufacture a quality product that was stable over time.

We did that recently with Prussian Blue for the indication for elimination of radiation from the body after accidental exposure. So we published a Federal Register notice saying that we had reviewed the scientific literature and concluded that Prussian Blue was safe and effective for that use, and now we're looking for manufacturers to come in and basically do the manufacturing package, the CMC package.

DR. JACOBSEN: Okay. I think we have time for one more question.

(Participant speaking from an unmiked

location.)

DR. GOODMAN: Well, you know, I think the question, because that mic doesn't seem to be working, was about vaccine delivery devices, and we've actually talked recently about potentially having a public workshop about this. I think it's a very rich area.

I think there are several different technologies out there that are quite exciting that offer promise of more rapid or less complicated vaccine delivery.

I think with vaccines the general point of view has been that each vaccine is a new product, but I think just like a syringe is a vaccine delivery device, some of these formats readily lend themselves to multiple vaccines.

So we do want to both hear more broadly about some of the technologies that are out there being developed as was suggested and then discussion some of the regulatory implications.

But as I said, it is very exciting. When you think of, for instance, we've had

discussion about this, you know, there are issues in the Third World about reduction of needle transmission of infections, and potentially some of these devices if they were not too costly could have tremendous promise in alleviating global health problems.

There are some suggestions that some of these devices may be able to deliver equivalent immunogenicity at lower antigen levels. That's a hope. So I think it's a very exciting area, and as I said, we may be able within the next year or so to be thinking about a workshop just on that subject.

DR. JACOBSEN: Well, it's five o'clock, and the agenda promised that you would be out by five.

I'd like to thank all of the panelists, and also I'm sure that if you have individual questions, they probably would be willing to hang around for a few minutes if you want to grab them before they can get out the door.

I don't know if there are any other wrap-up comments. Are there any other wrap-up

comments?

(No response.)

DR. JACOBSEN: Okay, and I'd like to say again thanks to Mariam and to Vickie for putting on such a good workshop in such a short time.

(Applause.)

(Whereupon, at 5:05 p.m., the meeting in the above-entitled matter was concluded.)

CERTIFICATE

This is to certify that the foregoing transcript in the matter of: Workshop on Delivery Systems

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represents the full and complete proceedings of the aforementioned matter, as reported and reduced to typewriting.