

## **FDA CDRH Webinar: A Dialogue between the Diabetes Community and FDA**

**Moderator: Irene Aihie**  
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**1:00 pm CT**

Coordinator: Welcome and thank you for standing by. Your lines will be in a listen-only mode until the question and answer portion of today's conference. If you would like to ask a question you may press Star and then 1 to queue up for questions. During today's conference a Web cam will be shared. In order to see the Web cam full-screen please go to the top right of your screen and click on Participants to view the Participants tab and then click on the Arrow icon in the top right of the preview in order to move the video to a full-screen view. You may exit the full-screen view by clicking on the Exit Full-screen View button in the top right.

I would now like to turn the call over to Irene Aihie. You may begin.

Irene Aihie: Hello and welcome to today's FDA Webinar. I am Irene Aihie CDRH's Office of Communication and Education. The focus of today's Webinar is to share general information about how the FDA regulates diabetes devices and about ongoing efforts to accelerate the availability of artificial pancreas devices. The conversation will focus on current and emerging artificial pancreas technology and the FDA's role in the reviewing of these technologies for safety and effectiveness.

Your discussion leaders are Dr. Courtney H. Lias, Director of the Division of Chemistry and Toxicology Devices in the Center for Devices and Radiological Health and Mr. Bennet Dunlap, President of the Diabetes Patient

Advocacy Coalition. Following the discussion we will open the line for your question. Stayce Beck, the Branch Chief for Diabetes Diagnostic Devices at CDRH will join our presenters for the Q&A portion of this Webinar. Now I give you Bennett.

Bennet Dunlap: Thank you very much. It's really a pleasure to be here when I want to thank FDA for making time to communicate with the patient community. That's not unusual. Your teams have been really generous with your time. I know Dr. Beck was out at CWD Friends for Life at Falls Church and I know that our friends from the Nightscout group recorded some of that and put that up on their Facebook page. And I think that's a great resource and I would encourage people to go get information there as well so thank you. Let's just get right in it. Why don't you tell us a little bit of about your role at FDA, the history of regulating devices and how you help products come to market?

Dr. Courtney Lias: Sure. Once again I'm Courtney Lias and I'm Director of a Division within FDA's Center for Devices. And in our division we regulated a lot of things. We regulate pregnancy tests and drug tests and tests that are done as part of the panels of tests that doctors order may order for liver, you know, liver toxicity or kidney disease or something like that. But another very large area of the work in our group is diabetes. So we regulate glucose meters, we regulate continuous glucose monitors (CGMs), hemoglobin A1C testing and also artificial pancreas devices and other devices that are similar on that scale.

Bennet Dunlap: So artificial pancreas means a lot of different things to different people. There's all kinds of screens going on right here. But what was confusing I feel like I'm going to enter Starship Enterprise in the Index. Anyway so artificial pancreas what does it mean to you guys and what does it mean in the (unintelligible)?

Dr. Courtney Lias: Sure. I mean I think the term artificial pancreas is one that's been used in a lot of different ways. People first started talking about this, you know, ten, 15 years ago or more and when they did that, you know, there was a lot of evolution in the way people talked about artificial pancreas development. You know, there was a lot of discussion I'd say about ten years ago about the different phases that devices would have to go through and that we wouldn't be able to get to a fully closed loop artificial pancreas device all at once for example. And so people were postulating that well first we will be able to do very simple things like suspend insulin delivery. And then we'll be able to do something slightly more complicated like go to a wide target range, just prevent extreme highs and extreme lows and then maybe narrow that target so that we really try and keep people at a very narrow range. And that would be sort of the ultimate goal. And then also have things like by bi-hormonal artificial pancreas that may be increase the level of control.

And the thought at that point in time historically was that, you know, this was sort of a natural progression in the technology development of the artificial pancreas. But I think that we have come to realize in the last five years, which I think is a very good thing, is that you don't have to follow that particular type of progression. That the types of technology we have now and the leaps that have been made by the investigators in the field have enabled us to potentially skip some of those steps and actually get to some of the closed-loop products that will help patients.

Bennet Dunlap: (Unintelligible) close...

Dr. Courtney Lias: I think so too. So when people talk about artificial pancreas devices that include things such as the insulin suspend devices, I think some of that's historical, so they're included as "artificial pancreas." So, you know, we can

be more specific and talk about closed-loop insulin delivery or bi-hormonal, you know, pumps that...

((Crosstalk))

Bennet Dunlap: I think there is a great deal of progress, you know, in thinking of that continuum as all related. And I know that when the guidance was out a few years ago there was separate guidance for low glucose then and then what was going to be artificial pancreas. But it seems to me that FDA sort of said well we want to look at these things as a whole and get in get into that process where the devices are as opposed to like creating two camps and...

Dr. Courtney Lias: Right, right.

Bennet Dunlap: ...you know, add regulatory burden to figure out what camp you're in.

Dr. Courtney Lias: Sure. So well I'll add something there. I mean many people may be aware that a few years ago we put out an artificial pancreas guidance document. And...

Bennet Dunlap: I think I know one or two people who read it.

Dr. Courtney Lias: So but many of you may not be aware that that type of guidance is not a usual guidance for FDA. So a lot of times what FDA does is they will wait until we have a lot of experience with the device type and then write a guidance and tell people okay now we understand what you should do to develop these devices or study these devices or show that they're safe and effective. And so it usually comes after the devices are on the market and there are one or more of them available. The Artificial Pancreas Guidance document was actually meant to be a forward-looking guidance. So it was put

out, and it's not something we typically do, but it was put out in order to look forward to promote the development of an artificial pancreas. And as such, you know, we sort of had to make some guesses on the types of things that might be available, but we also didn't want to limit what manufacturers or developers might want to do. And so it meant to provide a lot of flexibility in terms of one, how people define the devices that they make, and then two, what those devices are designed to do and how they show they are effective.

((Crosstalk))

Bennet Dunlap: So let's talk about that a little bit more because I know that I thought that was really interesting from the draft guidance to the final guidance. The draft had a lot of conversation about A1C and the final guidance seemed to be much more open to other endpoints. Can you talk a little bit about those endpoints and how that helps you work with developers?

Dr. Courtney Lias: Sure. And, you know, I would say the guidance process helps us to get that sort of progression and thinking. The guidance process allows us to hear from patients, from investigators, from the community on what they think is important. And so we did get a lot of comments of about the types of endpoints that might be appropriate in studying artificial pancreas devices. And I think it's clear that there are a lot of useful capabilities of products and that they may not all have to reduce A1C to be helpful to patients and improve safety or to give them more effectiveness, or even to stay the same but provide a better quality of life.

Bennet Dunlap: Yes I think it's fabulous.

Dr. Courtney Lias: And so...

Bennet Dunlap: ...that burden of care type consider (edging) as part of the final guidance...

Dr. Courtney Lias: I mean...

Bennet Dunlap: .....as part of what you guys are looking at.

Dr. Courtney Lias: ...Diabetes has a huge burden of care. I mean the amount of thought that has to go into, you know, just the care of anyone with diabetes whether it's themselves or their family members - if any of that could be lessened, you know, maybe they could concentrate on, you know, making, improving the care that they're giving with that extra energy or maybe enjoying a new hobby or, you know, just feeling a little bit more normal than they might normally feel.

Bennet Dunlap: So there's a lot of people trying to make these devices. You are open to a variety of endpoints. One of the things that our good friend (Kelly Klose) always talks about is that insulin is a very dangerous drug. So how in this process does that get factored into? So really what I'm saying is, you know, if I put one of these on my kits how do I know it's going to be fixed?

Dr. Courtney Lias: Right. So I think some of the things that people think about when they think of FDA regulation, it's really about that the clinical study that's done. And they pretty much only think of, you know, proving that a device works. But what they don't think about are some aspects of FDA's regulation of devices that may be less well-known. So some of the other things that we do is that we ensure that devices are made under what we call a quality system. And that quality system has a lot of different aspects and those aspects are intended to assure or to lessen the probability that something may go wrong.

So when you're talking about somebody designing a device for automated insulin delivery that you're right, insulin is a dangerous drug. And so if the device does what it's supposed to do presumably the insulin would be delivered in the way the device designer intended it to do but these devices contain software. They may contain complicated hardware and all software has bugs.

So how well the developer of that software follows certain types of practices reduce the likelihood of unintentional but very serious bugs in the software for example that might unintentionally deliver extra insulin when somebody might not want it or for example if the device just has some other design feature that will make it so that the insulin cartridge actually empties a little bit faster than it's supposed to, you know, even just processes like that part of FDA's regulations ensures that manufacturers follow very specific and methodical ways of ensuring that those risks are addressed as well as possible so that it's not sort of the wild West of, "Oh we think we wanted to make this better so we're going to make this change," and not realizing that change may have an impact somewhere else.

Bennet Dunlap: So it's a whole process of logging and tracking change and...

Dr. Courtney Lias: Yes.

Bennet Dunlap: ...creating accountability for that. So I know that you guys have different classes for devices. I may be one of the few people that knows that. I'm not sure that I know what the difference between Class I and Class II and Class III is so can you please give us a little bit of a rundown of those classes and where artificial pancreas would fall into that classification process?

Dr. Courtney Lias: Sure. I think many people when they think of FDA really think of the drug approval process and they think of, you know, many years of many different clinical trials and at the end of the day you get an approved drug. Well device development isn't really like that and also device regulation wasn't tailored that way either. So device - medical devices are a really big category and they include things like tongue depressors and hospital beds.

Bennet Dunlap: And lancets.

Dr. Courtney Lias: And lancets, a different conversation.

Bennet Dunlap: I'm sure everybody's just got a comment in. That's about today's conversation.

Dr. Courtney Lias: But it also includes artificial hearts and, you know, stents drug-eluting stents and things like that. So the way that you would regulate a tongue depressor should not be the same way that you regulate a drug-eluting stent and so we have different categories. So a Class I device is the lower risk category. And those devices typically don't even need to come to FDA before they go on the market. The manufacturer may have to do certain of those manufacturing steps that I mentioned earlier. They have to follow that quality process but they don't have to get FDA approval for marketing.

The Class II device is sort of the moderate risk category. And a lot of the diabetes devices fall into this category so insulin pumps and glucose meters are typically Class II devices. And they do have to provide FDA with information to support their marketing. So they have to come to us before they go on the market. So it's sort of a shorter timeframe and the types of timeframe and types of data give us are relatively well-defined.



And what they have to do is this is a little bit of a strange historical remnant from Congress. When medical devices were starting to be regulated in 1976 Congress said anything that's as good as the device on the market today should be able to be on the market tomorrow. And so these Class II products have to show what's called "substantial equivalence" meaning they have to show that they're as good as a device that's on the market already and so it's really more of a comparison. Is my glucose meter as good as a glucose meter that you cleared last year? Unfortunately it often means is my glucose meter is good as the glucose meter you cleared in 1985? So, you know, there's pros and cons to that.

Bennet Dunlap: Don't get me going on that. We already cover that one.

Dr. Courtney Lias: And then the PMA (Premarket Approval Application) process is somewhat similar to the drug processes in that you have to prove safety and effectiveness. But it's different in that the route that the technology gets there in terms of demonstrating safety effectiveness isn't so structured as it is in drugs. And that's where like we talked about the artificial pancreas guidance. That's where we can insert that flexibility. What is your "intended use," we call it. What do you plan to do with your device? What are you saying it can do and then that may determine the endpoint and how you're showing that it can do that. And sometimes that, you know, may not be very much information to send FDA and sometimes it may be a large clinical trial, so it really depends on the device.

Bennet Dunlap: So that's interesting because it's going to depend on device - a device. We know at least people that are proclaiming that they have devices in process, we don't really know if they brought them to you or not. I mean you're not allowed to say and we don't want you get into trade secrets but you see common commonalities in the products that have come to you to do

automated delivery and are you finding that there are regulatory processes that you can use consistently across the board?

Dr. Courtney Lias: Yes. And, you know, historically I think we were in a phase for the last maybe ten or 15 years where, you know, first the investigators and then increasingly the manufacturers were really trying to tweak their algorithms and make them. But about a year or year and a half ago there was sort of a very tangible switch in the discussion. And now the discussion is very excitingly much more about commercialization. And so we're talking to a lot of companies and developers about the artificial pancreas devices and some of them are farther along.

I think it's fairly common knowledge that Medtronic has a device that's just finished a pivotal trial. A pivotal trial is usually the main trial to hopefully support approval. And so presumably they would submit their PMA and, you know, we would take a look at that. And so, you know, then you have other products that may have been studied a lot in the academic community and need to be sort of realized into a commercialized product. And so the pace of this development has really increased and we're very happy to see that.

Bennet Dunlap: So one of the things I've heard you and Dr. Beck and actually people from the industry talk about is before they get into these trials you're open to working with the firm to help define the trial. Can you elaborate a little bit on that and - or is that happening and is it feeding across (unintelligible)?

Dr. Courtney Lias: Dr. Beck is the Branch Chief for our diabetes diagnostic devices branch and that branch handles all of these products. And...

((Crosstalk))

Dr. Courtney Lias: ...her group works tirelessly. They have a lot of these submissions. We have what's called a pre-submission. I know it's kind of a strange name but basically what it is is the manufacturer can ask us questions so they don't waste money on things they don't need to do or they don't waste money on a study that was designed the wrong way. And so we can sort of come to an agreement up front and that makes the back end where we get the product to look at a lot more efficient. We already know what they were planning to do and hopefully they've just done it and now we look at the results and that's really what we're focusing on.

So it's a lot of resources on our end and on the, you know, the developers, manufactures and but I think it helps because what like I said when it comes in the door we already know what to expect and that makes things go faster here.

Bennet Dunlap: So let's talk a little bit about these trials and it, you know, you've talked about academic trials and pivotal trials. Are there instances where, you know, somebody stubbed their toe in that process? I mean I obviously I don't want you to talk overly specific but is there a generalizations that could be made that can help enlighten people with diabetes on a process to get some feeling of comfort about what's going on?

Dr. Courtney Lias: Yes.

Bennet Dunlap: Like are you finding mistakes? Are you finding like strengths? Are you finding things that are common between different processes? Well what can you say?

Dr. Courtney Lias: Well when I mentioned before that over the last ten years the investigations have sort of been more academic. They've been developing an

algorithm. It's not FDA that's making them go back and do another small study and another small study and another small study. Typically what happens is they develop their algorithm and when they do a study in patients they see something that they didn't want to see, that maybe it's not behaving in the way that they would like it to behave. And so they learn something about the algorithm and they change it a little bit because they may have designed it knowing the patients they studied last time and they put it in five more patients they see something different because each patient is different and the algorithms don't work the same way in each patient. And so they're trying to optimize the algorithms for, you know, as broad a population of patients, or to define the types of patients that they could put on the label and say, "this is the type of patient that this algorithm is appropriate for and this type of patient it would be dangerous for use in," for example.

So we had instances where investigators have been doing clinical trials on their algorithms. And those trials have - are designed such that the patients are monitored fairly closely and that's for safety. So these devices are dosing insulin with sort of an unproven algorithm and in most cases everything is fine and there's no issues. But there have been cases where the developer did not realize that there was one of those software bugs I mentioned earlier. For example maybe there was a situation sort, of a specific combination of events that they didn't anticipate in their software development, that when that happens the last insulin doses are not tracked and the algorithm is trying to give the same dose over and over again. This is just a hypothetical example but it very quickly tracks some that we've seen.

So when they have seen this in the trials there were no injuries luckily because those trials were being monitored and they noticed this was happening while it was going on and they were able to stop it.

Bennet Dunlap: So the trial's...

((Crosstalk))

Dr. Courtney Lias: (Unintelligible) delivery...

Bennet Dunlap: ...(unintelligible) what it was supposed to do.

Dr. Courtney Lias: Exactly. And so they were able to investigate the cause of the overdosing of insulin and adjust the algorithm and the software to fix that bug so that the commercialized version won't do that to multiple patients who aren't being monitored and cause a lot of problems.

Bennet Dunlap: It was fascinating. There was a roundtable that Fall - the children's diabetes session at Falls Church and there were two academic now commercial developers there. And they both said that it wasn't FDA that was holding up the process. In fact that the process isn't being held up that FDA wasn't a drag. It was consistently, you know, they needed to go re-fix something or they needed to get something through an academic IRB board. And I think that's something people need to hear that the process is methodical and careful on all sides and, you know, safety quality...

Dr. Courtney Lias: Yes.

Bennet Dunlap: ...are near and dear to my heart so yeah.

Dr. Courtney Lias: Well I would insert though I think one of the concerns that the other side might think of there is a concern that if we're too methodical then, you know, we're not considering that we need this and it could save lives also. And so what's the balance? I do want to make the point that though these

investigators are making these statements and are carefully trying to develop these, neither their goal nor our goal is “perfection.” So we don’t expect that these devices will be perfect when they go on the market. We just want them to be reasonably safe and at least reasonably well understood to prevent as many, you know, serious...

Bennet Dunlap: Right.

Dr. Courtney Lias: ...injuries or deaths.

Bennet Dunlap: Well in diabetes there's nothing perfect about to start with.

Dr. Courtney Lias: Right.

Bennet Dunlap: So you talked about labeling and intended use. So can you comment on age? Is there a label for ages and does that impact how you look at a device because...

Dr. Courtney Lias: Yes.

Bennet Dunlap: ...you know, my kids were pretty young when they were diagnosed and there's always that process...

Dr. Courtney Lias: Right.

Bennet Dunlap: ...what about the peds?

Dr. Courtney Lias: I think there are a lot of perceptions out there that FDA is afraid to study these devices in children and in fact I think the opposite is true. What we're finding is the manufacturers are hesitant to try to do the trials in children

because they're difficult. We're - we've been in telling manufactures of artificial pancreas devices that they need to include children, young children in their trials because we know that these devices will be used once approved in children whether they're approved for that or studied for that or not. And a couple of reasons for that that we think it's important to emphasize at this point.

One, you know, a parent can then see, "yes, this device has been evaluated in another 3-year-old child and so I can at least have confidence that, you know, major issues might have been identified in these trials if there were some." Two, we know that there are differences in performance of all the currently available CGMs between children and adults.

So if you optimize your algorithm using data from a CGM in adults it will work differently in children. Have you accounted for that in your algorithms? And so what we're usually doing is talking to manufactures emphasizing one: don't plan to study this only in adults, and two: let's talk about how to maybe phase in children in your trials. Start with ten patients or so, get them so far into your trial, make sure there's no major issues with your algorithm and then start the kids, or something like that. So we usually try to work it in that way.

Bennet Dunlap: So you mentioned differences in centers. And it kind of raises an interesting question about these systems are a mismatch of components and what happens if there's an upgrade, you know, bump or the CGM or some other part of the process? Does the whole thing have to come back and be re-approved? Is there going to be a process for slotting in a more accurate, in a sensor or a different sensor or how's that at all...

Dr. Courtney Lias: So...

Bennet Dunlap: Or if you can (unintelligible)?

Dr. Courtney Lias: This is actually an area of really great interest for us and something that we're going to be embarking on a wider sort of effort on coming up soon. So currently the situation is is that if you have a manufacturer that makes all these components the situation is fairly easy for them. You know, they can control what they're doing with the CGM. They can control what they're doing with the pump and the algorithm. And, you know, the process is fairly smooth.

And from our end it's fairly smooth also because they send us one submission, they've covered all the bases. You know, if they upgrade that's just part of their process and part of their - our interactions with them. And on the marketing side if a patient has an issue then calls to complain it doesn't fall through the cracks because there's only one person to complain to.

But that scenario is not effective for promoting the development of artificial pancreas devices and it's not effective for what you're saying which is improving these artificial pancreas devices once they're on the market in an efficient manner. And so what we are trying to do now is to talk to the community about how do we get from the point where we have all these devices that don't talk to each other but don't have common ways of sharing information and how do we make them more what we're calling "plug-n-play"? How do we make it so that CGMs can be designed such that they might fit into any artificial pancreas system and pumps may be designed so that they could be used in different artificial pancreas systems and how do we make sure that there are no cracks to fall into between the manufacturers let's say, the algorithm, the CGM and the pump? And right now the infrastructure doesn't exist for that yet.



But if you think about it here, I'm not a camera expert but what I'm learning is when digital cameras first came out there were a lot of different formats for images. And quickly that particular field got to the point where now when you buy a digital camera and you plug it into the computer it will work with any image software. It will work with any printer, it will work with any computer. You plug it in, that image just pops up. That's kind of what we want with diabetes devices. We want if you have a CGM and you have a phone that they will work together somehow and that you won't have to buy a particular phone for example with your CGM. Maybe you can buy the phone you want. You know, that's the goal.

Getting there we have to put in this infrastructure to make the communication protocols the same to solve issues of different manufacturers having different types of data that aren't read by other devices or aren't interpreted by other devices and then having standards on what is sent. Is the glucose value sent or is the raw signal sent and if so are there different things that the individual manufacturers may have to address?

But the take-home messages here, you know, what we're going to be telling industry is we have to get to the point where regulatory-wise we can have clear, smooth transparent pathways for manufacturers to do this without having the rigmarole of having to create months and months of lawyer discussions to get contracts between two different companies that make two different things, and difficult post market situations, you know, "who's responsible when something goes wrong? The CGM manufacturer, the pump manufacturer, the algorithm manufacturer?"

Bennet Dunlap: So, you know, we've talked about manufacturer so and I know there's, you know, a couple hundred people on the call. A bunch of them are going to want

me to ask about what about the do-it-yourself community and how do you do that?

Dr. Courtney Lias: Sure. I mean I think the first way we view it is with empathy. If I were in that situation and for example my child or myself had diabetes (I don't, but I know people who do) and I understand the desire. So, you know, what they're doing is something that we can easily understand why they want to do that. But then the question becomes, you know, what will FDA do, you know, where's the point at which FDA will not be tolerant of this activity and a couple people really want to know or one of the things they may want to know.

So, you know, this effort first started with a secondary display of CGM values. And when we went out in public and talked about that what we said was sort of the risks were a little bit lower in that scenario. You know, there is less actionable issues that you can do. You're not controlling anything so you may be able to take some actions like calling the person or going and helping somebody who needs help.

And so, you know, the risk of that community developing sort of open source software for that type of thing were such that we did not exert our enforcement, you know, options on that. But we've been consistently saying that as soon as we get to the point where somebody is distributing information about, you know, automated insulin dosing or making artificial pancreas systems that are more distributed that's when we feel the risk is higher and we may enforce, you know, sort of to make it a level playing field. You can be a manufacturer and make an artificial pancreas device, or you might be a person (private citizen) and do that.

If you're doing it, if you're creating an algorithm and using it on yourself, that level of risk is different than if you're creating an algorithm and then sharing it with someone else. That algorithm may have been developed and optimized for you and it may not be actually an appropriate algorithm for somebody else. And that's why those clinical studies are done by the investigators and by the manufacturers of the artificial pancreas devices to find those bugs and to find those aspects of the algorithms that aren't suitable for wide use.

Bennet Dunlap: Or what I think I hear you saying is you don't want to have a level playing field and whether someone's manufacturing something for commercial distribution or some other model of distribution it still needs to go through the same consistent safety process?

Dr. Courtney Lias: The same requirements still apply. So, you know, one message that I want to send is that we're not saying you can't do it - you absolutely can. You absolutely can use a device, develop your algorithms and create an artificial pancreas device. But there may be FDA regulatory requirements that apply to you. You may need to get approval. You may need to get permissions to run a clinical study, or you may need to, you know, talk with us about what those requirements might be.

I think that if you're developing an algorithm for yourself and you're not giving it to anyone else that might not be the highest priority for us. But when it's not for yourself or, you know, somebody directly in your care like your small child, the risk is much different from our perspective. And, you know, a lot of this goes to a few things. You know, this issue about who's the responsible party. You know, in this scenario if this software is being created by a community, is there somebody really tracking the design of this product as it changes? Is there somebody who is really tracking whether or not the

changes that are being made may have downstream effects that might be detrimental to somebody else?

There's the issue of sort of "human factors" which is, how can the device be misused? Have those risks been thought of? So this came up in our discussion on insulin dosing calculators a couple of years ago where we talked about these apps that were designed such that you could scroll between doses and a dose of ten was right next to the dose of one. And if you sort of just miss hit that it's not a very good design of the app. And the same thing may be true by some of these, you know, that's the type of analysis that somebody's do when they're developing, you know, something for people to use, you know, how might they miss-use it because they will and...

Bennet Dunlap: Yes. And here's another part of the fun conversation. There's sort of a trade-off between the importance of securing data and I'm sure that there's people listening that understand it completely better than I do. So forgive me if I asked this question wrong. But what's the trade-off between data security and open format so that patients can get their data and do this...

Dr. Courtney Lias: Right.

Bennet Dunlap: ...themselves?

Dr. Courtney Lias: Like you I'm not an expert on cyber security. However luckily FDA does have experts on cyber security. And I hear from them and others that just because it's open source doesn't make it insecure. So that's not sort of the necessary thing...

Bennet Dunlap: Right. And I didn't mean to imply that they were.

Dr. Courtney Lias: Yes.

Bennet Dunlap: I was really asking two questions...

Dr. Courtney Lias: But that's something that...

((Crosstalk))

Bennet Dunlap: ...(unintelligible) sorry out there if I came across wrong.

Dr. Courtney Lias: No I think that sometimes a commonly held belief that if it's just out in the open it must be less secure. I understand that's not true although I could not give you the details. So, you know, we have a couple of things. 1) FDA is definitely interested in cyber security. We have a guidance document that applies to all types of things including diabetes. There are groups out there in the public, and we are sort of interacting with them, who are looking at cyber security specifically for diabetes devices. The Diabetes Technology Society, for example, has a group that is looking into this. And it is related to this interoperability piece I think. And the standards being developed for sort of remote pump controls that they're looking at developing to help sort of with this interoperability piece. This cybersecurity standard is intended to make sure the pump is actually getting the right, you know, commands and that those commands are secure for the right pump, and for the right person, is something that I think they're still working on. So we've been talking with folks there. But I don't think we should look at it as a barrier. I mean I think these things are solvable. I think the tools that lots of industries use for security can be easily incorporated into diabetes devices without slowing down development.

Bennet Dunlap: So one of the things that I've had people ask is how can you have a device that delivers insulin based on CGM data if CGM isn't labeled to deliver insulin? It sort of seems like a conundrum. How does that work?

Dr. Courtney Lias: Well so the artificial pancreas devices, the algorithms are actually developed with this technology. They were developed knowing the limitations of CGMs and pumps. And so the algorithms themselves sort of take into account what they can expect from these products. So it's a little bit different. You really can't consider the way that the system of a CGM, an artificial pancreas algorithm kind of pump work together as being the sort of the same as how you might look at them separately.

But on a related note certainly people are interested in using CGMs, you know, what we call a replacement claim. So in place of their blood glucose meters. And we have a submission from Dexcom in-house right now, and yesterday we announced that we'll be having an advisory panel meeting on that product July 21 here in the DC area. And it's an open meeting, and certainly I think Bennet can send out for somebody...

Bennet Dunlap: Yes we'll make sure...

Dr. Courtney Lias: ...might send out...

Bennet Dunlap: ...that people can find the information.

Dr. Courtney Lias: ...the link yes.

Bennet Dunlap: So let's can we just digress for one second and...

Dr. Courtney Lias: Yes let me...

Bennet Dunlap: ...not everybody may be able to get to DC.

Dr. Courtney Lias: Sure.

Bennet Dunlap: And if we all did you wouldn't be able to accommodate us all. So is there a process where the patient community can share their views...

Dr. Courtney Lias: Sure.

Bennet Dunlap: ...prior to the meeting?

Dr. Courtney Lias: And to clarify Dexcom is requesting this replacement claim. So there is in the agenda for the users there's typically one hour for anyone in the public to sort of request to speak. And instructions for that are in the link that we can send out. That hour is' divided by the number of people who want to speak. And so if we get more than a certain number of requests we can't actually accommodate everybody on the agenda although they can still submit their comments, you know, to the docket. So it's kind of like a guidance document and has a docket.

So there's a couple of things: if people want to organize together and submit, you know, a single comment with a lot of signatures that's one thing that people do to say, you know, "this comment represents 5,000 of us" or whatever it may be then. You know, it would - it could be read at the public meeting, the panel meeting to the panel. And, you know, that could be discussed how many people support that comment. That's one option.

If all sort of 5,000 people request to speak they probably won't all be able to. And, you know, it would be maybe one comment throughout the whole period

instead of a whole lot of different comments with different perspectives or stories that would be able to be shared. So, you know, it's just the other thing you can do is you can send written comments to the docket. And if you send them beforehand we can get them to the advisory panel prior to their discussions.

Bennet Dunlap: So that actually may be useful for patients to send comments in ahead of time so that members of the panel can consider them while they're considering Dexcom's submission.

Dr. Courtney Lias: That's right.

Bennet Dunlap: Not that I'm advocating for that right now, stay tuned. So I understand that in July there's going to be an industry meeting about artificial pancreas. Can you tell us what that's going to be about and what the expectations for that are...

Dr. Courtney Lias: Sure.

Bennet Dunlap: ...and how we can listen in and...

Dr. Courtney Lias: So this meeting is cosponsored by FDA by the NIH and by the JDRF. And this I believe is the fourth in the - a series of meetings like this that we've had every few years. And, you know, I'm happy to say that each time we have this meeting we sort of progress in sort of the development of our artificial pancreas. I can remember the first one where they were really talking about, you know, very, you know, getting into people basically, getting "how do we even start to study this in humans." And now we're to the point of, you know, "what's happening with the ones that are going to be on the market?" so it's very exciting.



So this is a very scientific type of meeting where the investigators and the companies come to talk about issues with the purpose of figuring out how to move this technology forward, you know, topics such as, you know, how do we think about using this in, you know, pregnancy? How do we think about, you know, this - what special issues may need to be considered for children to make sure we can have these products as quickly as possible for kids for example?

Bennet Dunlap: And are these for their write-ups to this process to reporters and public or...

Dr. Courtney Lias: So NIH is the primary organizer and we participate in that. I can't remember if they publish. I'm looking at Stayce.

Stayce Beck: Not that I know of, but Kelly Close and Adam Brown will be there and will publish a summary.

((Crosstalk))

Bennet Dunlap: So there's the answer right here. Diatribe will keep us well up to speed. Thanks (Adam) and (Kelly). I think I'm out of questions that people sent me ahead of time so maybe we should see if there's some online?

Irene Aihie: Operator we'll now take questions.

Coordinator: Thank you. If you would like to ask a question at this time we will be taking questions by phone only. To ask a question you may press Star and then 1 on your phone. When prompted to record your name please record your name and your company so that your question may be introduced. If you would like to ask a question again you may press Star 1. If you find you would like to withdraw your question from queue you may do so by pressing Star and then

2. Our first question is from (Matt Presnow) with Perception Builder. Your line is open.

(Matt Presnow): Yes. Hi there. I think this is a great opportunity that you're providing the public with. So first of all thank you for that. And then I'm sure this is going to come across as a total layman's question but given that burden of care and the risks of managing diabetes can't the FDA review process be shortened by leveraging the review and validations of pumps for artificial pancreas is in foreign countries where things like auto suspend are already in use? I mean it's 2016 and we have PDAs the know my child is going low. But her hump - but her pump is just going to keep on giving her insulin. I think that at this point waiting causes more risk than anything.

Dr. Courtney Lias: So I think that's a great question. And we do actually absolutely consider the level of risk that people face every day in making our decisions. We make approval decisions on a benefit risk balance. And so, you know, we sort of subtract the baseline risk from those decisions which really allows us to get patients products more easily I think.

We can leverage data from other countries in Europe. You know, people with diabetes aren't different, you know, in other countries. And so we can certainly do that and we're happy to do that. We talk with companies about that. We are limited though in that we can only clear or approve or review products that are sent to us. So if a manufacturer does not send us a submission, we can't approve it. We can encourage that they send it to us, you know, we can talk to them about it but we won't be able to do that.

(Matt Presnow): Is there a reason why somebody like Medtronic wouldn't have submitted an auto suspend at the same time that it was hitting the Europe given that the market in the US is going to be larger?

Dr. Courtney Lias: I mean I definitely couldn't speculate on Medtronic's reasons for choosing to put products in different countries. I do know that the requirements in some countries for certain types of products are lower than they are in the US in that in some companies for example for glucose meters they don't have to do, you know, any clinical studies to put a glucose meter on the market in Europe whereas they do have to do so here. And, you know, so but I certainly encourage you to talk to Medtronic about their reasons for that sort of thing. They don't often share them with us.

(Matt Presnow): Okay I just have one more quick one. What's the soonest that you think an artificial pancreas will actually hit the market? And then a follow-up to that is the soonest for a dual hormone artificial pancreas? This is the question you've been waiting for I know.

Dr. Courtney Lias: I mean, I think the publication on those sort of things are pretty exciting. So the dual hormone bi-artificial pancreas publications from a couple years ago got a lot of people very excited and certainly got some discussion going in terms of people who like it and people who don't like it. The drug that they want to use in their bi-hormonal artificial pancreas is not approved in so they have to develop that drug, you know, into a (commercializable) version in order to do that. So I think that that one will probably take a little longer.

I mentioned earlier that Medtronic has just finished their pivotal trial. They've put that in the public domain. So one would hope that if they put together a high-quality submission that's clear and gives us information there, you know, it does not actually take us very long to review that information.

So we mentioned earlier we work with companies ahead of time. We've been working very closely with Medtronic trying to speed up their timeline. A few

years ago we met with them and said, "Hey what will it take to get a closed loop device out on the market sooner?" And, you know, we worked with them and we said, "Why don't you, you know, skip some products and go to a closed loop? Why don't you - why are you waiting to do this?" And so we worked with them and were able to come up with a trial design that could be done faster and that's what they've done. And so we're very familiar with the trial and so hopefully we will be able to review that quickly. In the lifecycle of a device FDA reviews are not typically the long process. Often it's the development of the device at that company. So hopefully the - once they send it we will hopefully be in the home stretch.

Bennet Dunlap: And in fairness to FDA that's probably a question that they can't legally answer. I mean they may know things that they're not allowed to say. I think a really great resource to help give us clarity to answer your question -- and it may not be a satisfactory answer but it's what you can get -- is the conversation that was in the roundtable at Friends for Life of Falls Church there were two commercial developers there. They were pretty free with their comments. And I'm pretty sure (Wes) put them up online. And I'm sure our friends that are online right now from the we're not waiting group can find them and bump them up to the top of that Facebook page. And you can watch the videos. It's pretty interesting stuff and let the manufacturers speak for themselves I think is what I trying to say in a long-winded way.

Coordinator: Thank you. The next question is from Tom Lai with the National Federation of the Blind. Your line is open.

Tom Lai: Thank you. And I appreciate the forum being made available today. I – my focus is I think a little bit related to the interoperability question. For decades now so many of the D devices have been labeled not intended for use by people who are blind. And it's, you know, it's been a growing issue as people

are getting older who have Type I and are just, you know, getting age related eye issues. I think there's a tendency or hesitancy among manufacturers to even delve into this area because they believe of there will be a massive amount of additional oversight or regulatory impact or proof in order to open up the label to allow people who are blind to use the devices. I know with interoperability you spoke earlier there are plenty of smart phones available that can be used. And I think a natural first step pathway would be to have a smart phone that a blind person can use, be able to operate the insulin pump for the artificial pancreas.

What from the FDA's perspective would be the additional burden for a manufacturer to be able to place that on the label or remove them from the label that it's not intended for people who are blind? Thanks.

Dr. Courtney Lias: Thank you. And actually I really want to thank you for bringing that, you know, topic up because I think it's not something that's brought up very frequently to us. So to hear that perspective is really helpful and something that we can sort of more actively ask the manufactures about.

With regards to what they would have to do it depends a little bit on the design of the device and what - and how it's operated and how much the operation of the device relies on sight. And then, you know, certainly what the manufacturer would have to do would depend on what needed to be changed or validated to show that. In some cases I think it would be nothing. I think in some cases somebody who is blind might be able to be, you could just sort of do an analysis, what we call a risk analysis, and show that someone who is blind would be reasonably likely to be able to use the device as well as people who are not blind, or that maybe that there are acceptable devices available to aid in the use of those things.

Most of the time manufacturers, you know, have not assessed that in their development. So like I said I really appreciate you bringing this up because this is something that we can ask them about and see is it just something that they've been considering? Have they identified, you know, particular risks for use in the blind? Or is this something that they just wanted to disclaim so they didn't have to think about that into their design? So we will try to do that.

Bennet Dunlap: You can tell them thanks that's a great question. And at the risk of you be an advocate on FDA's clock I would love to have you send comments to that effect into the meeting on dosing or replacement because that's what I'm supposed to say right, replacement of CGM...

((Crosstalk))

Bennet Dunlap: ...(unintelligible)? I think that would be a very valuable comment and I encourage you to send that in. Thanks.

Coordinator: Thank you. Our next question is from (Ellen Allmond) on behalf of herself. Your line is open.

(Ellen Allmond): Hi. I'm wondering a long time ago when 21 years ago when my son got a pump it was a Dexcom come and it came as a two pump system. And I'm wondering if FDA can mandate that there will be a two pump two AP system because people will not be able to simply go back to a syringe and glucometer when there's a mechanical failure. So is that something that FDA could consider mandating when these AP systems are approved?

Bennet Dunlap: Hang on we're turning a microphone on.

Stayce Beck: Hi. This is Stayce, sorry. We have not really talked about mandating that companies provide an extra pump. What a lot of companies have - and I understand that this can be burdensome for people. I actually have a friend who has diabetes who was complaining on Sunday because it was Memorial Day the next day and she was telling me that her unnamed pump company pump broke down and she wasn't going to be able to get it until Tuesday. So we do understand that sometimes there is delay but a lot of the pump companies do try to overnight pumps, you know, so that they can - so the patients can get it if they're - for some reason there pump is not working appropriately at that time. Understanding that of course it is quite a burden to go back to using syringes and dosing that way.

Courtney Lias: I would say it's an interesting question too in terms of what will happen in the future when, you know, these closed-loop products become more normal. And if people - as people rely on them more, you know, I think that the conversation has to consider this and whether or not, you know, that will be acceptable. So it's a good point to bring up. Thank you.

Bennet Dunlap: So would that potentially be a human factors consideration that - what happens if it breaks?

Courtney Lias: Right. I mean one of the questions for example is, you know, if this becomes in the future so common that newly diagnosed people are put on it more quickly, you know, people who don't understand how to deal with diabetes on their own, you know, this risk changed a little bit then of somebody who's been dosing themselves for years then gets on an artificial pancreas if it breaks down they don't know what to do. If somebody has been relying on this then there is a little bit of a knowledge gap potentially. And we have to think about how the community would handle that type of situation.

Bennet Dunlap: So would that - would FDA be able to consider the distribution model as part of an approval? Like if say (Dennis Dunlap) artificial pancreas company did a deal with a national pharmacy chain and distributed through that pharmacy chain so that you didn't have to have one FedEx'd from our office you could go to the local, you know, Bob's pharmacy to get one.

Courtney Lias: Right. Well I mean I do want to emphasize I don't think we would start, you know, implementing lots of requirements that aren't necessary. So I'm talking about the scenarios, and that may be a future hypothetical scenario where this becomes a new risk that should be addressed. If there's a risk that should be addressed for patient safety we have mechanisms for doing that to enable patients to get what they need.

For example maybe the device wouldn't be safe and effective without this backup system or maybe if it's not Class III, maybe it's one these Class II devices, we put in sort of a requirement that you have to do X, Y or Z. So it's possible to do. But we would only do that in the scenario where we thought it was necessary for patient safety, and probably the community would have already weighed in on that, like we're hearing here some questions about it.

Bennet Dunlap: It's a real interesting question. Thank you.

Coordinator: Thank you. Our next question is from (Nancy Murphy) on her own behalf. Your line is open. (Nancy) please unmute your line or pick up your handset.

(Nancy Murphy): Hello.

Coordinator: We can hear you ma'am.



(Nancy Murphy): Hello okay. My question had to do with the messages that appear on the CGM for example where it gives pediatric recommendations. And I just wonder why those messages have to appear there as compared with in the documentation that accompanies the materials because I'm not a pediatric user of it. My child is but on my device it would be nice if there was some sort of adult versus peds or age group or something that you could enter on it so that it doesn't keep providing that message over and over again. The FDA says that you have to do this that or the other or not use this data if it's a pediatric situation. And so I just wondered why do those messages have to actually appear on the device itself?

Dr. Courtney Lias: Is this a Dexcom sensor?

(Nancy Murphy): Yes.

Dr. Courtney Lias: Yes so I mean I actually do think they have a pediatric version that doesn't have those alarms. And then second they have actually gotten approval of the different version of the algorithm that can be upgraded that doesn't have those warnings either. So I definitely would contact Dexcom to see if you could get the upgraded version of the software.

Stayce Beck: Yes. This is Stayce. The warnings were originally there because when Dexcom first did their studies of the previous algorithm they really did find that there was a big difference in how the CGM performed in children. And so they wanted to make it clear that, you know, if you were using that in the trials that you understood that it really didn't necessarily perform as well. And I think over time they've really been able to develop a system so that it performs a lot better so they no longer have those inaccuracies.

Dr. Courtney Lias: Right that's - I want to end with this. That's the power of the algorithm. The same sensor, the same signal coming off of that sensor, the same information coming out of the body with that software algorithm they can actually make that a lot more accurate so that's great technology at work.

Coordinator: The next question is from (George Natchel) on his own behalf. Your line is open.

(George Natchel): Yes thank you so much for taking my call. And, you know, I know the FDA gets a lot of bad press but man just listening in on what you're saying and the safety concerns you have I really, really appreciate that as a father of a Type I diabetic. Thank you.

Courtney Lias: We appreciate hearing that. And, you know, we appreciate both sides. If people think we're going too far but also, you know, if there are concerns that they want us to know about that's how we learn them. So this type of conversation is extremely valuable to us.

(George Natchel): Yes. No thank you. I just had a couple of quick questions. One so my son right now just has the CGM. He has Dexcom. He has to calibrate at least four times a day. I don't know a whole lot about the artificial pancreas the closed loop system. Will that require the same kind of a thing where you still calibrate like with a CGM and those other parts to it as well?

Dr. Courtney Lias: So it will depend on, you know, the system eventually that you would have. And, you know, if it's using some of the current sensors you could probably expect the calibrations would be similar to what they are today. I think Medtronic has two a day is that right?

(George Natchel): Okay.

Dr. Stayce Beck: A minimum of two a day but...

Dr. Courtney Lias: Recommended to four. So but all of the companies are trying to work on what they're calling factory calibration which would make it not necessary to calibrate with a glucose meter. Right now the sensors are more accurate when they calibrate that frequently so that hopefully they'll be able to figure out a way to do it at the factory so that each sensor is calibrated and you don't have to do that. So that's just the goal. They're working hard on it.

Bennet Dunlap: And if I could jump in and say that it would be great to get to the new calibration point. What I find encouraging is that we're finding ways that have safe or reliable automated insulin delivery with the tools that we have now and it can only get better so also (George) great to be hearing from another dad of kids with diabetes.

(George Natchel): I appreciate that. And then I guess my last question was going to be -- you probably can't answer this -- I was going to say is two years a reasonable expectation? Not to nail you on anything but I mean is that reasonable the way things are looking or is that something that can't be answered?

Bennet Dunlap: Right let me answer that because it isn't fair to ask the FDA that because they can't answer it. So I would suggest that careful listening to the commercial communications from these companies suggest that that is a realistic expectation in that timeframe subject to approval.

(George Natchel): And you mentioned on Facebook that one group. What was it I'm looking for specifically for a video on there? I miss that part, sorry.

Bennet Dunlap: So the - (Wes) was down from the Nightscout group was at the CWD conference in Falls Church Virginia where we the Diabetes Patient Advocate Coalition had the pleasure of hosting a roundtable with Dr. Beck, JDRF and two device manufacturers. And it was just an open conversation and I encourage you to hunt that down. And we will make sure that there's a link on the Diabetes Patient Advocacy Coalition Facebook page and Web page to help you find that. (Wes) can you send me a link? I know you're out there listening somewhere.

Irene Aihie: We'll take the next question.

Coordinator: The next question is from (Debra Leib) with Music by (Debra). Your line is open.

(Debra Leib): O hi, a couple of my original questions were answered by listening. But one of them was the artificial pancreas. It seems like that's what the pump is being called when it actually is not an artificial pancreas. So are you - to me a closed loop system would be an artificial pancreas. So...

Bennet Dunlap: Yes.

(Debra Leib): ...I don't know why they just don't call them pumps because that's what they are. But there's a couple of really cool places that are really close to a cure. One of them is at Miami University. They actually had someone that has this type of pouch where it has some insulin cells in it or I mean some isolate cells in it. And - hold on. She's been without insulin for like almost a year, well it's been about six months. Are you familiar with that study?

Dr. Courtney Lias: So I am not familiar with the study itself but I am familiar with in general studies on islet cells and that is actually overseen by FDA's Center for

Biologics. And, you know, we work with them here and that group actually works really hard to try and help with those. I think they've made a lot of advancements. They've really got to work on, you know, making those islets last so it's really encouraging that you're hearing that your friend or colleague is doing well with that.

Bennet Dunlap: Yes. And the point is...

(Debra Leib): No, no it's not a colleague of mine.

Bennet Dunlap: There isn't a simple solution and the idea is that sensor augmented pumps using an algorithm which is what an artificial pancreas would be in this context or in the context of this conversation is a step. But it's only an interim step towards ultimately a cure. But better is better and I think that everybody's encouraged to know that our friends here at FDA and our friends in industry are working hand in glove to get us to better so that we can have better before there's a cure.

Dr. Courtney Lias: Yes. And I know that there will be even the closed loop devices that are farthest along they're not no-intervention. People will still have to, you know, bolus for meals and treat their diabetes. So there are steps to go but, you know, we hope that that these devices are effective and safe that they will be very helpful to people.

Bennet Dunlap: And they can be a step towards feeling better. Thanks.

Coordinator: Our next question is from Manny Hernandez with Livongo Health. Your line is open.

Manny Hernandez: Hi. How are you Courtney and Stayce and Bennet. Thank you so much for doing this. My question actually may take longer to answer than we have time left so I'll just like leave it as a topic or an idea maybe for a future Webinar. I would love to hear your thoughts or the agency's general thinking regarding the other type of potentially helping close the loop that is like the area where we start, you know, seeing more smart pens and other insulin delivery devices aided by digital tools to help, you know, that side of the equation which has not necessarily been addressed or in today's Webinar. So if you can speak briefly to that if not like maybe in a future Webinar about it would be lovely. Thank you so much again for all you're doing.

Dr. Courtney Lias: Thank you. I actually think that you're right. It might be sort of its own topic. I actually suggest why don't you send me an email with the types of questions because some of the things that you're mentioning involve people that haven't been involved in this Webinar. And so we can get them involved and potentially get the questions that you have answered so please send them to us. The email on the screen (dice)@fda.hhs.gov they - you can send those to us and we will, you know, we will be happy to try and see if something can be done there.

Bennet Dunlap: I would love to hear that too.

Coordinator: The next question is from (Margot Kane) on her own behalf. Your line is open.

(Margo Kane): I actually have two questions. The first question is the size of this artificial pancreas that's being tested will it be able to be used with children from the age of 7 or 8? When do you foresee it getting to a size that would be appropriate for them?

Dr. Courtney Lias: So I mentioned earlier that we're really telling manufacturers you need to study your devices in children, don't just ignore it. So either know that your device is unsafe in children and make sure that that's clear to people that it's unsafe and why it's unsafe. One example of why something might be unsafe is that maybe it's like you said not sized correctly or maybe, you know, it's doses too much insulin for small children or something like that.

So when a closed loose device is cleared is approved by FDA it will have a label and that label will specify the age range that it's approved for. A lot of these devices like we said are used off label. We're really trying to get companies to study them, you know, down to 2 -year-olds because we know that 2-year-olds have diabetes too. So that will be clear and it may be different for each device depending on how it's designed but we see the need in children as well. We don't think these devices should only be developed for adults.

Irene Aihie: Operator are you there?

Coordinator: Yes. Did you want to take any further questions at this time or should we refer questions to the email address listed on the slide?

Irene Aihie: That will be the conclusion of our question and answer.

Coordinator: Thank you. This concludes the question and answer for today's session. If you would like to send in a question you may use the email address that is listed on the slide in the WebEx presentation. And this does conclude today's conference. Thank you for your attendance. You may disconnect at this time.

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