FDA Webinar: Consideration of Uncertainty in Making Benefit-Risk Determinations in Medical Device Premarket Approvals, De Novo Classifications, and Humanitarian Device Exemptions - Final Guidance

Moderator: Irene Aihie
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Coordinator: Welcome and thank you for standing by.

Today's call is being recorded. If you have any objections you may disconnect at this time.

All participants will be in a listen only mode until the Question and Answer session of today's conference. At that time you may press star 1 on your phone to ask a question.

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

Irene Aihie: Hello. And welcome to today's FDA webinar. I'm Irene Aihie of CDRH's Office of Communication and Education.

On August 30, 2019 the FDA issued the Final Guidance Document, Consideration of Uncertainty in Making Benefit Risk Determination in Medical Device Pre-market Approval, De Novo Classifications and Humanitarian Device Exemption.

This guidance outlines a rigorous, methodical approach for the consideration of uncertainty when assessing benefits and risk of a medical device and for

determining when it may be appropriate to shift some data collection from pre-market to post market.

This includes devices subject to pre-market approval applications, De Novo requests and humanitarian device exemptions.

Today, Charles Viviano, Medical Officer and Clinical Deputy Office Director for the Office of Gastrorenal, OBGYN, General Hospital and Urology Devices in the Office of Product Evaluation and Quality, and Pablo Morales, Chief Medical Officer in the Office of Clinical Evidence and Analysis, both here in CDRH, will present an overview of the guidance document.

Following the presentation we will open up the line for your questions related to the information provided during the presentation.

Additionally, there are other center subject matter experts here with us to assist in the Q&A portion of our webinar.

Now I give you Charles.

(Charles Viviano): Thank you Irene and welcome to our webinar presentation of Consideration of Uncertainty in Making Benefit Risk Determinations in Medical Device Pre-market Approvals, De Novo Classifications and Humanitarian Device Exemptions Final Guidance. For simplicity we will refer to it as the Uncertainty Guidance from now on.

Let’s review the agenda.

We will start by identifying the objectives for today’s presentation and provide some background on the rationale for this guidance, where

consideration of uncertainty fits in the overall assessment of benefit risk and how it supplements our perspective on benefit risk determination as proposed in our existing Benefit Risk Guidance documents.

We will discuss the scope of this guidance - where and when it applies and, importantly when it does not.

We will review the factors CDRH will consider when assessing whether additional uncertainty might be warranted and, if so, to what extent.

We will discuss the application of the principles of the Uncertainty Guidance in two scenarios (breakthrough devices subject to PMA and devices for small patient populations subject to PMA) where greater uncertainty could be appropriate and we will review examples.

We will also review mitigations to account for greater uncertainty and finish up by providing resources for you should you need further guidance on the Center's thinking on benefit risk for different submission types, in addition to taking questions at the end.

By the end of this presentation you should understand how uncertainty fits within the FDA's benefit risk framework, as well as the factors the FDA considers in assessing the appropriate extent of uncertainty about a device's benefits and risks.

Finally, you should understand how these factors are applied in two scenarios where greater uncertainty might be appropriate - breakthrough devices and devices for small populations.

This Uncertainty Guidance falls within the overall benefit risk paradigm the Center has described for various submissions through a number of benefit risk guidance documents and policies. The Agency generally provides marketing authorization for a device when it meets the applicable standards, including that its benefits outweigh its risks.

Consideration of the uncertainty surrounding the benefits and risks is something we take into account when making the benefit risk determination that is part of the evaluation of a device in a variety of contexts.

For example, FDA's final guidance on Factors to Consider in Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications ("PMA and the De Novo benefit risk guidance") includes consideration of patient preference and uncertainty in the process of making such determinations and provides a framework for benefit risk decision-making for these submissions.

These benefit risk guidances for different submission types and this Uncertainty Guidance complement each other in that benefit risk guidances list uncertainty as a factor in benefit risk decisions, while this guidance further clarifies how we determine the appropriate extent of uncertainty for a device at the time of designing the clinical data that will be used to support a future marketing application.

FDA's approach is tailored to the type and intended use of the device and the type of decision we are making. To provide clarity on how the FDA will assess for the appropriate extent of uncertainty when planning the collection of clinical data, we have identified factors to consider during this process.

Doing so provides a rigorous, methodical approach for the consideration of uncertainty.

In some circumstances FDA may accept greater uncertainty regarding the device's probably benefits and risks when appropriate because of the greater probable public health benefits of earlier patient access.

Further, it may be appropriate to collect additional data in the post market setting, rather than pre-market, to address the greater uncertainty about the device's probable benefits and risks provided that the statutory standards for pre-market approval are met. This is the so-called "pre-market, post market data shift".

The appropriate extent of uncertainty in clarifying the clinical evidence needed to support pre-market decisions is flexible and depends on a number of factors including the device type, patient population characteristics, the intended use of the device, and the type of decision the FDA is making, among others.

This is not necessarily a new concept. This guidance provides a framework for that flexibility when determining what data collection is appropriate at the right time.

To better articulate FDA's policy on its decision making in various other contexts across the total product life cycle, including with respect to other types of submissions for devices, FDA has published several guidances that demonstrate a flexible, patient-centric benefit risk approach, including the consideration of patient preferences and uncertainty.

This Uncertainty Guidance fits within the agency's benefit risk paradigm and further clarifies assessment of the appropriate extent of uncertainty when designing the clinical evidence needed for PMAs, De Novos and HDEs.

These aforementioned guidances take into account the uncertainty inherent in the totality of evidence regarding probable benefit risk. This includes identifying when it would be appropriate to include risk mitigations and the collection of post market data within its authority to address uncertainty in benefit risk information.

There can be varying amounts of uncertainty in benefit risk information received by the Agency. Uncertainly can be inherent in the collection of clinical evidence. We identify uncertainty in the information we are given as arising from various sources.

There can be uncertainty around the type, magnitude, duration, frequency and other aspects of a device's benefits and risks to patients. Other sources of uncertainty in clinical data include patients lost to follow up, missing data, protocol deviations, and underpowered pre-market studies without subsequent post market studies.

In addition the policies in this guidance further FDA's mission to promote the public health by fostering medical device innovation and facilitating timely patient access to high quality, safe and effective medical devices by acknowledging and addressing uncertainty upfront.

In addition, the principles described in this guidance aim to assure greater transparency, predictability, consistency and efficiency using least burdensome principles.

The tenets of this guidance apply to the generation of clinical evidence at the pre-submission and IDE stage in support of PMAs, De Novos and HDEs.

Examples provided of PMAs for breakthrough devices and PMAs for devices intended for small patient populations are illustrative but the application of this guidance is not limited to these submissions.

As stated previously, the appropriate extent of uncertainty is determined by many factors which we will review shortly. These factors help to determine whether, and to what extent, a pre- to post-market shift might be acceptable.

The pre- to post-market shift may depend, in part, on the magnitude of the probable public health benefit. For example, a greater data shift could be appropriate if the probable magnitude of the benefit is high as is the likelihood that the data can and will be collected in a timely manner post market.

A large data shift may not be appropriate if post market data collection is not likely to occur in a timely manner or at all.

The FDA has identified the following factors to provide a transparent and methodical approach to assess the appropriate extent of uncertainty in developing the clinical evidence required to support a marketing application.

The following factors are taken directly from the guidance.

First the extent of the probable benefits of the device, taking into account the type, magnitude, probability, duration and frequency of those benefits, including if the probable benefits are greater than those of approved or cleared alternative treatments or diagnostics or the standard of care.

This first factor is an assessment of the probable benefits of the device including whether the benefits are greater than those of currently approved or cleared alternatives.

You may notice we are talking about probable benefits here, because at the pre-submission or IDE stage of development data demonstrating benefit may not be available.

Next, the extent of the probable risks of the device, taking into account the severity, type, number, rates, probability and duration of those risks, including if the probable risks are less than those of approved or cleared alternative treatments or diagnostics or the standard of care. This is essentially the same concept as the first factor but addressing the probable risks.

The next factor is the extent of uncertainty regarding the benefit risk profile of approved or cleared alternative treatments or diagnostics or the standard of care. For example, the strength of the evidence supporting the alternative treatment or diagnostic.

In other words, how much uncertainty has the FDA already accepted in our approved or cleared treatments. For various reasons the FDA may have accepted additional uncertainty in assessment of benefit and risk when reviewing a marketing application.

For example, if the device was intended for a very sick population with few treatment options or for an HDE.

The next factor is patients' perspective on appropriate uncertainty about the probable benefits and risks of a device, if available.

Note, this is not assessing whether patients would choose this device over currently available options but, rather, what do patients think is the appropriate amount of uncertainty surrounding the device's benefits and risks. That is how much uncertainty in benefit and risk are patients willing to accept?

This is typically only available in well-conducted patient preference information studies. For further reference please see the FDA's Patient Preference Information Guidance.

The next factor is the extent of the public health need- for example, seriousness of the illness, benefit risk profile of other available therapeutics or diagnostics, if any, including the current standard of care and the portion of the target population for whom there would be a positive benefit risk profile.

This factor assesses the Big Picture surrounding the device and the indicated population (the illness, the alternatives available, who would benefit, et cetera.)

This factor allows consideration of multiple issues around the device and intended use which together may create a different perspective than any of these issues taken separately.

The next factor considers the feasibility of generating extensive clinical evidence pre-market based on appropriate considerations (for example, taking into account the prevalence of the disease or condition).

By means of example, perhaps all stakeholders may agree that an appropriately powered randomized control trial would be appropriate. But

given the prevalence of the disease, the patient population, and other factors, is it likely that such pre-market clinical data collection would be feasible?

In some situations, it might be more reasonable to collect some data pre-market with additional post market data if such collection post market is feasible and likely, and there is still enough evidence overall, pre-clinical, clinical, animal, et cetera, to still meet the applicable regulatory standards for marketing authorization.

The next factor is the ability to reduce or resolve remaining uncertainty of a device's benefit risk profile post market (for example, consideration of the FDA's authority to require post market data collection and the likelihood that the necessary post market data collection will be completed within reasonable timeframes).

This factor addresses as to whether there is an advantage for pre to post market shift. But one must also consider the likelihood the necessary post market data will be collected. For example, if there were already a well-established registry that can provide the data.

The next factor addresses the likely effectiveness of mitigations such as labeling and other tools to help provide a reasonable assurance of safety and effectiveness of the device as applicable.

Can the additional uncertainty be mitigated (given there are advantages to accepting this uncertainty) through labeling or further refining the indicated population to one that is more likely to observe a benefit or might experience a greater benefit than a larger population?

Regarding labeling, where post market data collection is required as a condition of approval to address greater uncertainty in the device's probable benefits and risks, FDA intends to consider whether it would be appropriate (for example, whether it would be helpful to healthcare providers) to include as a condition of approval that the device labeling describe the post market data collection and its purpose.

Where applicable, FDA also intends to include such information in the Summary of Safety and Effectiveness Data (the SSED) and to flag post market studies that are condition of approval for the device on our Web site.

The next factor takes into account the type of decision being made. For example, there is generally likely to be more uncertainty surrounding a device's benefit risk profile based on the evidence submitted in an HDE application as compared to a PMA because the standards for approval are different. And this is essentially dictated by the different policy and statutory requirements for certain marketing applications.

And finally, the last factor considers the probable benefits of earlier patient access to the device. The FDA might be willing to accept more uncertainty to provide earlier patient access to a device. Again, this brings into consideration disease, current treatments available, the population that could benefit from earlier access, et cetera.

Finally, similar to the least burdensome principles, consideration of uncertainly as described in this guidance does not lower the bar for the evidentiary requirements as defined by the statutes for the respective type of marketing application.

The evidence supporting the device's reasonable assurance of safety and effectiveness must continue to meet the applicable regulatory standards for marketing authorizations.

And now I will turn it over to Pablo to discuss application of the principles of the guidance and to review the examples provided in the guidance document.

Pablo Morales: Okay. Thank you very much Charles. So now that we know the background and the factors that are outlined in this guidance document we are going to dive into the applicability of these.

One case where increased uncertainty might be appropriate is for breakthrough devices because by nature these devices have the potential to address unmet clinical needs in serious conditions and also because patients may be willing to accept greater uncertainty in the benefits and risks of such products.

As previously outlined by Dr. Viviano, to meet the statutory standards for approval including that the device's probable benefit out weigh its probable risks, the FDA may accept greater uncertainty regarding the device's probable benefits and risks when appropriate, because of the greater probable public health benefit of earlier access to patients.

However, if greater uncertainty is deemed appropriate, it is critical that the data collected in the post market setting is reliable, high quality and collected in a timely manner. Therefore, certain post market controls may be necessary like timely post market data collection, transparency and accountability.

Now I'm going to tell you a little bit more about these three mitigation strategies.

Timely post market data collection. We require a post market study as a condition of approval within a specific appropriate timeframe.

And second, we need to ensure that the FDA's expectation are explicitly fine-tuned in the 522 orders, and in the PMA and HDE conditions of approval, so that the agency will have certainty that these post approval studies are going to be conducted in a timely fashion.

The second mitigation strategy is transparency. Under transparency we expect the labeling to describe when post market data collection is required to address greater uncertainty and also include this information in the summary of safety and effectiveness or SSED, the Summary of Benefit and Probable Benefit or SBPB or the De Novo transparency summary.

And last but not least, in the mitigation for greater uncertainty we have accountability. The agency will hold an advisory committee meeting if there are outstanding questions about whether post market data continues to support a reasonable assurance of safety and effectiveness.

And also, taking into account committee recommendation and post market data, we will consider issuing a withdrawal order or certain restrictions on the sale and distribution or narrow the indication for use for a particular device.

Another case where additional uncertainty might be considered appropriate is on devices for a small patient population that are subject to PMA because of the rarity of the disease or condition, it is generally not feasible or it's also time intensive to generate extensive clinical evidence pre-market.

And also, there is an unmet clinical need that is addressed by the device, such as there are no available therapeutic or diagnostics for that patient population.

Similarly, when a device is not eligible for a breakthrough or HDE status we can consider these uncertainty principles.

And last but not least, while there is not a specific number of patients that will be considered as a small patient population, this approach could be used for patients with rare disease or conditions or for patients within a clinically uniform subset of a broader population.

Now I'm going to go through the specific examples that were outlined in the guidance document. Although these examples illustrate how uncertainty may be reflected in the confidence level of one sided significant level for a clinical study, we know that uncertainly may be reflected in many other ways, when appropriate and based on the circumstances of the given device technology. For example, by using a surrogate endpoints.

With that in mind let's describe the first example from the guidance document.

Example one is about breakthrough devices that are subject to PMA. The device is a breakthrough device that is intended to treat a currently treatment resistant condition. The performance goal is 70% in a proposed pre-market single study. And after an assessment for conventional, modest or high extent of uncertainty, the clinical trial will be reflected by the one-sided significant level and will be manifested in different sample size.

So when scenario one is conventional uncertainty based up on the factors outlined in the guidance document that were considered into this given

example and all the relevant information, the FDA is not willing to accept additional uncertainty in the pre-market study design and the one sided significance is 2.5%, the observed performance goal is 74% and the spec sample size will be 535 subjects to be 97.5% confident the performance goal is above the 70%.

Scenario two is about modest uncertainty. Based on the relevant considerations including the feasibility of a post market data collection, FDA determines that modest extent of uncertainty is appropriate. And this will result in a larger one side significance from 2.5 to 5% and lower confidence from 97.5% to 95%, which will result in a smaller sample size of 385 subjects.

The approach will include a post market study as condition of approval noted on the Website.

Now, suppose the FDA instead determines that, based on the relevant considerations and the factors outlining the Uncertainty Guidance, including that the sponsor has a reliable and appropriate mechanism to complete a timely collection of post market data. For example, a registry that meets the criteria outlined in real world evidence guidance document published in August 2017 an even higher extent of uncertainty may be reasonable.

Therefore, the example by modifying the one sided significance and the level of confidence will result in a sample size of 125 subjects to be 80% confident the performance goal is above 70%. The condition of approval that post market study is noted in the labeling, in the SSED and on the Website, as appropriate.

Now, example 2 from the guidance document is about devices for small patient populations that are subject to PMA. The device will be intended to

treat a disease with an incident of 10,000 new cases annually. This is not a breakthrough device because the disease is not life threatening or irreversibly debilitating. It's indicated for a disease that is serious but to which there are no available therapies and the acceptable performance goal is 60%.

So using the same approach as we did for the breakthrough devices, we are going to go through conventional, modest and high uncertainty.

Scenario one is about conventional uncertainty. Based upon the factors outlined in the guidance and all the relevant information, the FDA is not willing to accept additional uncertainty in the pre-market study design.

The one sided significance is 2.5%, the observed performance goal 66% and the expected sample size is 274 subjects to be 97.5% confidence that the performance goal is above the 60%.

Now, for the modest uncertainty similar to what we did with the breakthrough designation devices, we are going to increase the one sided significance alpha to 10%, we are going to lower the confidence level from 97.5% to 90% and the sample size resulting from this example will be 128 subjects.

Now modest uncertainty requires a post-market study as condition of approval noted on the Website. These pre-market to post market shift can be made possible if it is feasible to collect the post market data that the agency requires.

Last but not least the scenario 3, the high uncertainly is based upon the factors in the guidance document and all the relevant information that there is a reliable source of post market data like a registry.

The FDA is willing to accept additional high uncertainty in the pre-market study with a significant pre to post market shift when the one sided significance is 20%, the observed performance goal is 66%. We are going to be 80% confident that the performance goal is above 60% and that's going to take us to a sample size of 65 subject in the pre-market study.

Now, a robust post market study with reliable data source like from a registry needs to be in place and the condition of approval that post market study will be noted on the label, in the SSED and on the Website, as appropriate.

The following slide illustrates resources related to a benefit risk determinations throughout the total product life cycle in different circumstances.

So now we are going to open the line to start getting some questions.

(Charles Viviano): While the Operator is queuing up the questions one frequently asked question is, "Does the uncertainty guidance apply to 510(k)s that require clinical data," which is a small subset of 510(k)s? Because the evidentiary requirements and the regulatory requirements of substantial equivalence are different than for PMAs, De Novos and HDEs the Uncertainty Guidance as described here does not apply to those 510(k)s where clinical evidence is required.

Coordinator: As a reminder if you would like to ask a question over the phone lines please press star 1 from your phone, unmute your line and speak your name clearly when prompted. Your name is required to introduce your question. If you would like to withdraw your question please press star 2.

Again if you would like to ask a question please press star 1, unmute your line and speak your name clearly when prompted. One moment as we wait for any questions.

(Charles Viviano): Another frequently asked question while we are waiting is, "How are patients likely to be affected by the principles outlined in this guidance?"

The acceptance of greater uncertainty in pre-market submissions where the probable benefits outweigh the probable risks may translate to more timely access to new medical devices by making sure our processes are efficient and our regulatory frameworks are tailored to technology type and patient needs.

We believe we can garner the information about the safety and effectiveness of new devices in the pre and post market settings with less time and less cost while we are providing the assurances that patients depend upon.

Coordinator: Our first question comes from (Allison Komiami). Your line is now open.

(Allison Komiami): Hi. Thank you so much for this webinar. Very, very helpful. I have got a quick question about the breakthrough pathway and also whether or not this guidance document will also encompass the Safer Technologies Program when that becomes finalized?

Woman 1: This is Angie Krueger, Associate Director for Regulation Policy and Guidance. Excuse me in OPEQ. That's a great question. I think right now as you noted the Safer Technologies Program (STeP) is a draft guidance and a draft policy and will be looking at the intersection of that policy if it's finalized and these guidances.

You know, the Safer Technologies Program (STeP) is broader than some of the, you know, than the scope of this particular guidance as (Charles) noted. This is geared towards PMAs, HDEs and De Novos and the Safer Technologies Program (STeP) could be broader than those.

And so I think there are certainly things that are in the Safer Technologies eProgram (STeP) sort of be a final policy it would feed into this where considerations of uncertainty would be appropriate but they may not be a completely overlap to data set. And we will be looking at how that overlaps and how they feed into each other as we finalize the policy for the Safer Technologies Program (STeP).

(Allison Komiami): Excellent. Thank you so much.

Coordinator: As a reminder if you would like to ask a question please press star 1 from your phone. Our next question comes from (Andrea Mushen-Bourne). Your line is now open.

(Andrea Muchen-Bourne): Hi. What recommendations can you provide to determine how to balance the focus on uncertainty at the IDE level versus PMA for novel devices?

(Charles Viviano): So, this is Charles. I just want to follow up. So I think you are asking how to balance the uncertainty at the time of IDE development and the uncertainty at the time of the marketing application for PMAs. Is that correct or did I misinterpret your question?

(Andrea Muchen-Bourne): Yes. That's correct. My concern is that waiting until the PMA level might cause issues especially if it's a novel device which needs to - the uncertainty needs to be addressed sooner.

(Charles Viviano): Yes. And I think, you know, the Uncertainty Guidance is certainly trying to recognize that concern and to try to address that uncertainty earlier in the clinical data development phase.

This is a bit more - I understand your concern with regard to novel devices but hopefully identifying the uncertainty and addressing it earlier in the review cycle will be helpful at the time that we are at the marketing application because we will have made an assessment of uncertainty based upon the factors that we discussed this morning - this afternoon, I'm sorry, and sort of address those upfront.

And we will have agreed between the agency and the stakeholders with regards to acceptable and appropriate levels of uncertainty and their mitigations. Pablo and I mentioned mitigations for that additional uncertainty so that there is always going to be uncertainty at the time of the marketing application for reasons that I alluded to.

Clinical trials don't always go exactly the way we all envision them to go. There is loss of follow up, there are other things that happen during the conduct of the clinical trial.

If we were able to identify and address some of the uncertainty upfront we are hoping that we will have a better understanding of the acceptable and appropriate amount of uncertainty at the time of the marketing application.

Does that help or does that answer your question?

(Andrea Muchen-Bourne): Yes. Thank you.

Pablo Morales: This Pablo. In addition to what Charles just said I want to mention Andrea that we account for the uncertainty as much as we can using these principles

under the IDE phase. At the time of PMA we want to use the benefit risk guidance to see if the benefits of the device outweigh the risks.

Hopefully because we are using these principles of uncertainty prospectively through IDEs, if there is an occasion on which we are going to require a post approval study and there is no registry up and running, for example the Electronic Health Record (her) in the institutions doing the clinical study for the IDE, can be all beefed up to answer the safety and effectiveness question.

I think there is an opportunity to start working with the FDA proactively so that when the PMA comes along we have developed the landscape to collect that additional uncertainty because of developing a registry take times .

There will always going to be uncertainty but I think what this guidance is allowing us to do is to plan for uncertainty so that we have less challenges? at the time of PMA, number 1, and number 2 that if any post market mitigation strategy needs to be put in place we will start working on them upfront. Not the time of PMA when we don't have time to work with industry, professional societies, patient reps and all other stakeholders to for example develop a registry.

Those things don't fall from the sky and it takes time to build up a registry or a real world data source and there will be an opportunity to bridge the gap from the IDE phase so that when the PMA comes along you are going to have the certainty that the data is going to be collected and we will be reassured that the statutory standard of safety and effectiveness is going to continue through post market.

(Andrea Muchen-Bourne): Thank you.

Coordinator: Our next question comes from (Pamela). Your line is now open.

(Pamela): Hi. My question is specific to the De Novo process and I was wondering if you could share some best practices around providing the risk benefits summary to go in to the De Novo application.

(Angie Kreuger): This is (unintelligible). Thank you for your question. So I think that what we see in De Novos in particular because those devices have a different risk benefit profile than products that are reviewed under PMA. Those a low to moderate risk devices that could be placed in class 1 or class 2 with special controls if appropriate.

It's really being able to tell your story and outline in the context of the data collected for the device under review how you consider the benefits and the risks - how the benefits outweigh the risks and how any risks to health are mitigated by proposed special controls.

And so I think in the context of De Novo more uncertainty is certainly a part of that benefit risk calculation similar to PMA. Its presented in a different way and the mitigation is maybe different particularly for devices that may be of lower risk. The way that you outline how - what the clinical benefit is and how the benefits outweigh the risk may differ very, very greatly in terms of the different types of devices.

And to some of it that I think is helpful for reviewers is really being able to kind of outline how you think those benefits identified how you think the risks are mitigated and what calculus looks like really in kind of a story form.

(Pamela): Thank you.

Coordinator: We have no additional questions in queue. I will now turn the call back over to Irene.

Irene Aihie: Thank you. This is Irene Aihie. We appreciate your participation and thoughtful questions. Today's presentation and transcript will remain available on the CDRH Learn Web page at www.fda.gov/training/cdrhlearn on Thursday October 24.

If you have additional questions about today's presentation please use the contact information provided at the end of the slide presentation. As always we appreciate your feedback.

Following the conclusion of today's live webinar please complete a short (unintelligible) questions survey about your FDA CDRH webinar experience. The survey can be found at www.fda.gov/cdrhwebinar immediately following the conclusion of today's live webinar.

Again, thank you for participating. This concludes today's webinar.

Coordinator: Thank you for your participation in today's conference. You may disconnect at this time.

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