De Novo Final Rule
CDRH Webinar
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Moderators: Elias Mallis and Joseph Tartal

Elias Mallis: Greetings, everyone and thanks for joining us for today's CDRH webinar. I'm Elias Mallis, Director of the Division of Industry and Consumer Education in CDRH's Office of Communication and Education. And I'll be your moderator for today's program. Today's topic will cover the final rule and associated final guidances related to the De Novo program. These regulatory actions have recently been finalized, so we're holding this webinar to provide you with an opportunity to learn more about the efforts and to answer your questions as you consider incorporating future De Novo submissions.

It's my pleasure to introduce you to our presenter for today's program: Dr. Peter Yang, De Novo Policy Analyst and Program Lead in CDRH's Office of Product Evaluation and Quality, Office of Regulatory Programs, Division of Submission Support.

We'll kick off today's program with a presentation from Dr. Yang and then come back around for a discussion and field your questions about this topic. Thank you, Peter.

Peter Yang: Thanks, Elias. My name is Peter Yang. Again, I am the Program Lead for the De Novo program. And I reside in the Division of Submission Support in the Office of Regulatory Programs at CDRH.

So I hope at the end of today's presentation, you'll be able to describe the background and history of the De Novo program, describe the new De Novo regulations and how it might change or not change the De Novo review process, describe the contents of the updated De Novo guidances and what they cover, and then identify the contents of the updated De Novo Refuse-to-Accept checklist, otherwise known as the RTA checklist, and ultimately what is required for acceptance of a De Novo request.

There's a lot of information to cover today. But we'll have a question and answer session at the end where you can ask questions about the contents of today's presentation.

One thing I want you to keep in mind as we move forward is that everything that we're discussing today, the final rule, the updated guidance, and the updated RTA checklist, none of these things are for implementation until January 3, 2022.

So for any De Novo request received prior to January 3, 2022, we will review them under our existing policies, including the current RTA guidance and not the new RTA guidance that I'm going to discuss in this presentation.

I want to take a few moments here to discuss what a De Novo request is especially for those of you who might be unfamiliar with the program. So a De Novo request is a premarket submission. So if we grant your De Novo request, you get marketing authorization and can market your device.

However, the De Novo request submission type is intended for devices that are automatically classified into class III by virtue of not yet being classified. So here's what I mean. If a device is new to FDA where its particular combination of intended use and technological characteristics means that it's not

comparable to other devices, by statute it is automatically designated as class III and requires Premarket Approval, or a PMA, to be legally marketed.

But as you can imagine, not every new type of device has the same kind of risk profile that we would normally associate with the PMA level of device. And so a De Novo request does two things. First, as I just mentioned, you can get marketing authorization for your device. But the way that you get there is that you are actually requesting FDA to formally classify your device into class I or class II based on a determination of reasonable assurance of safety and effectiveness.

So it's not a substantial equivalence decision. We are not saying that your device is as safe and effective as a predicate device. We were actually determining that on its own, the De Novo device is safe and effective. So if we grant your De Novo request, FDA is giving you marketing authorization by creating a brand new classification regulation for your device. And then from then on, your device and future devices of the same type are now regulated through 510(k) instead. So the De Novo device that FDA reviews becomes the first predicate of its kind and then future devices will say that they are as safe and effective as your device and then continue to evolve that space.

So it's important to distinguish De Novo requests from other kinds of submissions or other kinds of things that you may hear about from CDRH, so it's not a kind of 510(k) submission. There's no such thing as a De Novo 510(k). It's not a substantial equivalence determination as we talked about earlier. We're not saying that this device is as safe and effective as a predicate device. It's not a premarket approval application either. It's not subject to the same kinds of approval requirements as what would be in a PMA. And so we don't say that a De Novo request is approved. We say a De Novo request is granted.

And then lastly, it's also not a 513(g) request for information. So a 513(g) submission is to request the Agency to identify what we think is the right review pathway for your device given some high level information about its intended use and technology. And so a De Novo request is the actual premarket submission to get marketing authorization. You can certainly submit a 513(g) before you submit your De Novo request. But a De Novo request is the actual submission to market your device.

So it's important to remember that when FDA is reviewing your De Novo request, FDA is actually performing a classification procedure to decide whether to classify your device into class I or class II. And so as part of any classification procedure, there are these three goals to meet. The first goal is to determine whether the probable benefits of the device outweigh the probable risks to health. This is sort of your standard benefit risk analysis.

The second goal is to identify what the probable risks to health are for the device or product when used as intended. And then based on the risks to health that we identify, determine the level of regulatory controls that are needed to mitigate that risk. And so if we only need general controls to mitigate that risk, that's class I. If we need a combination of general controls and special controls that makes the device class II.

And so general controls include things like registration and listing, MDRs, or medical device reporting of adverse events, labeling requirements, quality system regulation requirements. These are in place for a wide variety of medical devices. If we need special controls, that would be things like specialized bench testing that's specific to the device intended use or technology, specialized animal testing, clinical testing requirements, specialized labeling requirements specific to the device type in question, that would be class II.

And the majority of De Novo requests are granted as class II medical devices. So assuming that we meet all three of these goals together, that's what provides reasonable assurance of safety and effectiveness, and that's what allows us to grant a De Novo request.

Want to provide some brief background on the history of the program. The program was first created in 1997 but didn't really achieve full popularity until the advent of the direct De Novo option in 2012, which basically meant that you didn't have to first get a not substantially equivalent decision on a 510(k) first before you came in with-- before you could come in with a De Novo request. So after 2012, we saw the number of De Novos received by the Center increasing every year.

In 2016, we added the possibility for combination products to come through the De Novo process. In 2017, De Novos became subject to user fees and performance goals, and this resulted in new guidances for the program. We issued a final RTA guidance in September, 2019 to help govern the refuse to accept process for De Novos. And then it was all culminated in the De Novo final rule, which was published on October 5 of this year and again, does not take effect until January, 2022.

With MDUFA IV, the Medical Device User Fee Amendments, De Novos are subject to user fees. You can see here on the right which outlines the user fees and the small business discount for small businesses. User fees also result in performance goals based on a timeline of 150 FDA days. It's important to remember that this is different from the statutory deadline of 120 FDA days. This 150 day FDA timeline is negotiated with industry for MDUFA IV.

So in Fiscal Year 2022, De Novo has received during that Fiscal Year 2022, we intend to render a decision by Day 150 70% of the time. These performance goals are different compared to 510(k)s and PMAs largely because the De Novos are new to user fees.

And as I said before, we have seen increased use of the program over the past decade or so. So in Fiscal Year 2011, we received 19 De Novos. That has gone up over time. There was a huge spike in fiscal year 2017 because that was right before user fees were implemented. So everyone who submitted then was trying to get their De Novo in for free. And that's when we had 99 De Novos. And since then, we've fluctuated in the 60 to 70 range.

So it's important to remember that for the history of the program, the support that we have had to actually run the program has been in two places. One is the statute, Section 513(f)(2) of the Federal Food, Drug and Cosmetic Act, as well as for a long time, it was just the De Novo program guidance. So statute and a single guidance document, and that was it. That was what was there to support the program.

As part of MDUFA IV, we added new guidance documents around things like user fees. I'm talking about the FDA review clock and then the Refuse-to-Accept guidance issued in 2019. But what we really needed to sort of complete the picture for the De Novo program was regulation. Because without regulations, the De Novo program and the review process are being implemented entirely through non-binding guidance, through recommendations from the Agency.

So adding regulations provides clarity in the review procedures for De Novo requests, because the De Novo review process is now codified by these regulations. And so the regulations provide a regulatory framework for the De Novo program that's similar to 510(k) and PMA regulations. And once I show you and once we walk through the De Novo final rule together, you'll see how that is the case.

OK, so now it's time to talk about what's actually in the De Novo Final Rule.

So some of you may be asking yourselves a pretty obvious question, which is what is the De Novo Final Rule actually? The De Novo Final Rule adds new regulations to the Code of Federal Regulations called the CFR that governs the De Novo review process. So those of you who love medical device regulations may already know that the regulations governing medical device classification, those procedures are codified at 21 CFR 860. And so as because De Novo requests are medical device classifications, the De Novo regulations are now placed at Subpart D of 21 CFR 860.

So let's have a brief overview of what's actually in 21 CFR 860 Subpart D. It's 21 CFR 860.200 through 260. And as you kind of look through the elements here, you'll see that these are pretty straightforward outlines for how a De Novo request should proceed. So the purpose, the format, what should be in a De Novo request, how a De Novo request is accepted or reviewed, how a De Novo request is withdrawn, and then final decisions on De Novo requests, either to grant or decline.

So now, we're actually going to go through the individual sections of 21 CFR 860 Subpart D so that you can understand the regulations governing the De Novo review process. So 21 CFR 860.200 provides some brief background on the De Novo process, distinguishes between different kinds of De Novos including that direct De Novo option that we talked about earlier.

21 CFR 860.210 covers the request format at a very high level. It specifies it should be in electronic format, that it should be submitted in English, and specifies where to send the De Novo request for FDA to review it. 860.220 covers the required De Novo request content. And so this is what should be provided in every single De Novo request submitted to the agency.

A lot of this is pretty straightforward, table of contents, administrative information, regulatory history, the device name and indications, a description of the device, technical sections including non-clinical testing reports, software clinical testing reports, labeling, and bibliography. These are pretty standard requirements for medical device submissions submitted to the Agency.

The elements that I've highlighted here in blue are really more specific to the kinds of information that are really helpful for FDA to review as we make a De Novo classification decision, so things like alternative practices and procedures, what kinds of other devices are out there, how might this device fit into that. A classification summary, what kinds of other devices exist and why is this device different such that a De Novo request is the necessary review pathway for this device?

Proposed special controls, summary of risks and mitigations, all of those things that are necessary to support the classification procedure, what do you believe the classification recommendation? What do you believe should be the classification of the device, class I or class II? Benefit risk considerations, other information known to you that could be helpful in supporting FDA in making a determination of reasonable assurance of safety and effectiveness, a summary of the studies that you've provided, these kinds of information can really help FDA to make a De Novo request decision.

21 CFR 860.230 for the first time codifies the acceptance review process. Those of you who are familiar with medical device reviews at FDA know that 510(k)s, PMAs and De Novos all have a refuse-to-accept process that works pretty similarly across the different submission types. And so 21 CFR 860.230 codifies this into the De Novo review process, and the key concepts are the same and not changing.

So at a high level, when we accept your De Novo request, that means that the De Novo request contains the information necessary to permit a substantive review. So essentially, that means that the submission is complete, such as that FDA has everything we need to get started so that everything's there including everything in context. We intend to perform our acceptance review within 15 days of receipt. And if for some reason we fail to do so, the file is automatically accepted. So either way, you'll have an acceptance decision from us within 15 days.

860.230 outlines the acceptance process. Now, it does codify the acceptance review process. But really, this aligns with our current process for De Novo requests for the refuse to accept process as well as RTA policies for other programs. So really, there's nothing really surprising here. And let me just explain what that acceptance process looks like.

If we accept your file, that means that the De Novo request contains the information necessary to permit a substantive review. That basically means that everything is in place. You've had all of the data and all the content requirements from the previous slide. And so therefore, everything's in place for FDA to really see everything and to do a review of your De Novo request and use the time that's given to us appropriately.

We will perform this acceptance review within 15 days of receipt of your De Novo request. And if we don't contact you within 15 days regarding whether or not your file has been accepted or refused for a review, then the file is automatically accepted. So again, if you've ever done a 510(k) or a PMA before, they have similar refuse-to-accept policies, and ours is no different.

So as I said, we intend to refuse to accept your De Nova request if it is incomplete if it's missing information that we need to proceed with our review. However, there are a few other instances outlined in 21 CFR 860.230(c) where we will refuse to accept your De Novo request. So let me go through a couple of those here. So FDA may refuse to accept a De Novo request if you have an existing or open pending submission for the same device and indication.

And essentially what's happening here is if you submit a 510(k) and a De Novo request at the same time for the same device, that's a little bit confusing to us, right? One device needs to go through one pathway, either the 510(k) or the De Novo process. And so what we're going to do is put your file on hold until we can outline what your intent is and what the right pathway might be for your device.

We might refuse to accept the De Novo request if it's for more than one type of device. And so this is essentially where you're asking the Agency to perform multiple benefit risk analyses, generate multiple regulations, maybe you've got a whole bunch of different devices that you're asking FDA to review within the context of one De Novo submission. And so this really defeats the purpose of the user fee program. And so we would prefer that you focus your De Novo request on a single type of device such that FDA can focus and allocate its resources appropriately.

This is not by the way, this is not the same thing as saying that you might have a small, medium, and large size of your device. And so you're asking FDA to review those three sizes as part of the same De Novo request. We're not really talking about that example here. That's possible-- that's potentially possible to be reviewed under one De Novo request, right? This is really about asking the Agency to do multiple reviews under one single De Novo request.

And then lastly, we may refuse to accept the De Novo of a request if you have not responded to a previous deficiency. And so this is essentially where maybe we've interacted before on a previous De Novo request, or maybe there was a 510(k) or other kind of submission. And so before we proceed with review, we want to understand how you've responded to our past feedback, how you have addressed the deficiencies that we've identified earlier so that we sort of have that context for proceeding with this new De Novo request that we're reviewing.

21 CFR 860.240 outlines the procedures for a review of a De Novo request that specifies that review takes place in 120 days. That's a requirement per the Federal Food, Drug and Cosmetic Act. But I just want to point out that per MDUFA IV, our timeline for reviews is negotiated to 150 days. 860.240 also outlines the additional information request process. It indicates that we may put the file on hold to request additional information regarding deficiencies that we might have regarding your De Novo.

And then 860.240 also outlines our inspection authority, including that we have the authority to inspect your De Novo request for issues related to data integrity as well as a quality system inspection for critical or novel manufacturing processes. And here, I want to be clear that this is not our-- it's not our intent to inspect every single De Novo request as a matter of course. It's our intent to limit our quality system inspections for critical or novel manufacturing processes, and that's in the regulation.

So for specific instances in which there's something unique about your device technology or its manufacturing such that an inspection is really what's necessary for us to be able to understand the technology better and to ensure reasonable assurance of safety and effectiveness. In the past, we've publicly discussed a couple of examples. And I'll just go through those here. One example would be a novel sterilization process to where understanding your device is really critical to understanding how the sterilization process functions and how we can ensure that devices, products are appropriately sterilized within the sterilization, this novel sterilization procedure.

The other example that we talk about is a device-drug combination product where the device is combined with the drug and the manner in which it's combined, the carrier, the manufacturing are really critical to understanding how that combination product will function in practice. Looking at the elution profiles, looking at the pharmacokinetics, and so understanding the manufacturing process will be critical for us to have reasonable assurance of safety and effectiveness in that instance. So again, it's intended to be pretty rare and very limited to specific cases.

21 CFR 860.250 talks about the withdrawal procedures for De Novo requests. We consider De Novo requests withdrawn when you voluntarily withdraw the De Novo, when you don't respond to a refusal—refuse-to-accept decision within 180 days, when you don't respond to an additional information request within 180 days, or if you don't permit FDA to inspect facilities at a reasonable time and in a reasonable manner.

860.260 talks about making final decisions on a De Novo request whether that's to grant or decline. The way that the regulation is written is such that we grant a De Novo request unless there is a reason to decline, which may include things like deficiencies and so forth. So if there are no outstanding deficiencies, then we should grant your De Novo request.

It also specifies that we will publish a notice in the Federal Register to actually update the CFR with the new regulation including any special controls if it’s class II. When we grant a De Novo request, that De Novo device can now be used as a predicate for future 510(k)s. If instead we choose to decline your De

Novo request, we will send you a written order which includes all outstanding deficiencies that should be resolved before your De Novo request can be granted.

The 860.260 also specifies that we always make final decisions based on the classification criteria explained in 21 CFR 860.7. And as we talked about earlier, making decisions on De Novo requests, includes meeting all three classification goals, our benefit risk analysis as well as making sure that we mitigate outstanding risks to health with general and special controls.

21 CFR 860.260(c) outlines the potential reasons that we might decline a De Novo request. And there are a number of enumerated reasons in 860.260(c) which I'm going to group here for the purposes of generally explaining why we might decline a De Novo. So some of the reasons include reasons related to ineligibility, basically that it's either not a medical device or there's already existing review pathway for the device, whether that's through the PMA pathway or the 510(k) review pathway.

There are a number of reasons that are sort of more general in nature. Basically generally, it might not necessarily meet the criteria in section 513(a)(1) one of the Federal Food, Drug and Cosmetic Act for classification in class I or II. Basically, we can't write general and special controls to provide reasonable assurance of safety and effectiveness. There might be a false statement of material fact or a material omission in the submission, the labeling might not comply with 21 CFR 801 or in the case of in-vitro diagnostics, 21 CFR 809.

And then there are a number of reasons that we might decline, which are really related to the data provided as part of the submission. So it might be for reasons related to inspection results. It might be reasons related to good clinical practices or good laboratory practices such that the data are found to be unreliable or invalid. There might be outstanding deficiencies related to a clinical or non-clinical study, might not have been completed per the study protocol. Deficiencies may not be addressed. And so we have outstanding issues with the submission.

And this last bullet point here is in the case that a De Novo request is accepted, we've begun our review and then mid-review, you make significant unsolicited changes to the device. So you say, "OK, we don't want you to review the previously proposed indications for use. We want you to review a brand new set of indications for use. We want you to review a device with new technology. We've made some significant changes to the device. And we basically want you to kind of restart your review with a brand new device."

And in that case, that really puts FDA in a bad position. Now we have less time to review your device, and we're basically starting over from scratch. And so we might decline in that instance.

So that covers 21 860.200 through 260. There are a couple of other very minor editorial changes made to 21 CFR 860 just some updates the scope and definitions. We've also added confidentiality provisions for De Novo requests. We've always kept confidentiality for De Novos, but now we're codifying that, right? So basically, we don't disclose the existence of De Novo requests until a De Novo request has been granted.

So what are some distinctive elements of the De Novo Regulation and the De Novo Final Rule? One of the distinctions here is that the De Novo Final Rule specifies submission contents. So it specifies what should be in a De Novo request. It codifies the acceptance review process. So it actually has-- we actually have a specific section that lays out how a De Novo request should be accepted for review.

We also outline that we can refuse to review a De Novo request until it's administratively complete, until it includes all the elements, until basically everything's in place and ready for us to go. It adds specific inspection authorities for De Novos. And then it outlines specific reasons for declining a De Novo request including reasons related to eligibility, inspections, and then non-clinical and clinical data deficiencies.

OK, so along with the De Novo Final Rule, we have associated updates to our guidances for the De Novo program. The four De Novo guidances that I'm going to cover next are the De Novo Program guidance, the De Novo User Fees guidance, what I call the De Novo Actions Clock guidance, and the De Novo RTA guidance. And so the full titles of those guidance documents are there. And now we're going to go through each of them in turn.

So just to summarize the major changes here, the guidances have been updated to reflect changes for consistency with the Final Rule. But as you might have noticed as I kind of walk through the procedures for how we review De Novos, we're trying to align with our existing process, right? Those of you who have done a De Novo before probably haven't noticed really significant changes here.

And so changes to the guidance that are generally not substantive. Because again, the Final Rule really codifies in place of what we're already doing for De Novo requests. And so there are some minor updates to the guidances to reflect the Final Rule. Mostly it's the addition of a lot of references to 21 CFR 860 reflect the Final Rule establishing regulations for the De Novo review process.

The most significant change which we'll walk through in a little bit of detail is the updated acceptance checklist, which is now based on 21 CFR 860.220, which talks about the content and 230, which talks about the acceptance review process.

OK, so now let's go through each of these guidances in turn. The De Novo Program guidance, the purpose of this guidance is to provide an overview of the De Novo review process and what FDA does during the course of review. So we talk about things like eligibility, how we know that the De Novo process is appropriate for a device. We emphasize the importance of a presubmission or getting in touch with us early on to help make sure that the De Novo process is right for your device. We talk about the De Novo review process generally, and we explain what happens after a De Novo request has been granted.

Next, the De Novo User Fees guidance, we provide an overview of our user fee policy for De Novo requests. We talk about when you should pay for a De Novo request and how to pay the user fee for De Novo requests. We explain the refund circumstances. So in some cases we can authorize refunds for De Novo requests, and we explain that in this guidance. And we add some minor clarifications in our refunds policy. We always recommend that you submit your request for refunds as soon as possible and we kind of talk a little bit about that in the guidance document.

Our De Novo Actions/Clock guidance is intended to describe the actions that FDA and industry may take on De Novo requests and how those actions might affect the De Novo review clock. So we talk about FDA final decisions or interim and final decisions. So that's either to grant or decline to De Novo request or while we're in the middle of review to request information from you during the De Novo review process.

We talk about each reason why a De Novo made to be declined. We reference 21 CFR 862.260 there. We describe the industry actions on a De Novo request, so that's either submitting, withdrawing De Novo requests, submitting additional information, and so on. And we describe the De Novo performance goals to help clarify the timeline and what FDA will try to perform against.

OK, let's spend a couple of slides talking about the De Novo acceptance review process, the De Novo RTA guidance. So the purpose of this guidance is to help ensure that a De Novo request is acceptable for substantive review, that it's administratively complete, it's got everything, and it's ready to go for FDA. And so that helps facilitate an efficient and timely review on our end because we have everything we need to proceed when we get the De Novo request.

So again, as I explained before, this is similar to our policies for 510(k)s and PMAs. We will complete our acceptance review within 15 calendar days of receiving the De Novo. And if we don't complete our review within 15 days, then it's automatically considered accepted. There was a MDUFA IV commitment for the De Novo program that we create a submission checklist. And this De Novo RTA guidance fulfills that commitment.

OK, let's talk about some of the changes here. Because those of you who have done De Novos before might notice some differences between the current RTA checklist and the new RTA checklist that will be coming along with the final rules. So the current RTA checklist is actually split into two parts. So if you look at the RTA guidance that we have currently, there are two appendices. The first one is an acceptance checklist, which is actually required. That includes all the required content that we currently require for acceptance of your De Novo. And appendix B includes the recommended checklist.

So these elements are not required for acceptance of your De Novo request, but we would generally recommend that you include those elements anyway. The new RTA checklist requires all the content described in 21 CFR 860.200, so that's what we talked about on a previous slide. And so in doing so, in requiring all of that content, it essentially combines both the required and the recommended checklists. So now, all the elements from Appendix A and Appendix B essentially are now required elements for acceptance of your De Novo request.

So the current checklist includes requirements for items such as the intended use, the device description, your proposed special controls for the device. And now the new checklist adds items such as prior submission, so help us understand the regulatory history of this device and your previous interactions with us, an eligibility analysis, how have you determined that your device is eligible for De Novo classification, and finally, the device labeling.

So interestingly, we could not require that sponsors provide labeling for their device in a De Novo request. And now with this updated checklist, we can now require that sponsors provide their labeling. Now, obviously most companies would provide labeling anyway. But now we can actually require that it be provided.

So you've seen this slide before. I'd like everybody to keep in mind that the Final Rule, the updated guidances which we just talked about and the updated RTA checklist, none of these items are for implementation until January 3, 2022. And so for any file received prior to that date, we will review your De Novo request under our existing policies, under our current RTA guidance.

And in fact, actually, if we've published both the current and the updated RTA guidances side by side on our website. And you can see that link there, and we'll also be at the end of this presentation. So that you can see them side by side and prepare for the change. You can understand what elements might be required by the updated RTA checklist if you're going to submit after January.

OK so what's next for the De Novo program? The next thing that I want to highlight is eSTAR, otherwise known as the Electronic Submission Template and Resource. Basically what eSTAR is is a smart PDF checklist that helps prepare submissions for review by FDA. And so this has already been in place for traditional 510(k)s, and now we're planning an eSTAR for De Novo requests. So we anticipate the official De Novo eSTAR to be available to use after January 3, 2022.

It's been updated to reflect the items that will be required by the updated RTA checklist. So if you fill out the eSTAR completely, if everything checks out, and the eSTAR PDF document has ways of ensuring sort of that your file is complete that you've included all the necessary elements, then it should pass the acceptance review process. And take a look at the voluntary eSTAR program web page for more information about what's coming for eSTAR for De Novos.

Lastly, I just want to leave you with some helpful links to some De Novo resources so you can always read the Final Rule in the Federal Register. You can read our central web page for the De Novo classification request process, which includes the guidance links to the guidances that we just talked about at the bottom of the web page. So that can be a handy one stop shop for you.

We also have our transparency web page, which lists all of our most recently-granted De Novos. As well as our canonical database, which you can search to see all the De Novos that FDA has granted in its history. This page here lists all the resources that we've discussed today, so all of the links to all the documents and other resources that we've talked about are all here on this particular slide.

If you have any questions, you're welcome to email me directly. My name is Peter Yang, and my email address is Peter.Yang@fda.hhs.gov. You can also direct any questions you have to the Division of Industry and Consumer Education at DICE@fda.hhs.gov. We're here to help you in preparing your De Novo request.

Here is a summary slide for you that kind of addresses the learning objectives that we talked about earlier at the beginning of the presentation. Hopefully, if you've gone through the slide deck with me, and you read through this summary, you'll be able to complete your learning objectives for this presentation. So thanks very much, and I look forward to hearing from you soon .

Joseph Tartal: OK, thank you Peter for that excellent and comprehensive detailed overview of the De Novo program. You covered a lot of ground for us. So I'm going to do a quick introduction. My name is Joseph Tartal. I'm the Deputy Director in the Division of Industry and Consumer Education. And I'll be moderating this Q&A portion of the program. So as we transition to the Q&A segment, I'd also like to introduce some of our FDA discussion panel that will be joining Peter and answering your questions.

First, Josh Nipper, Director of Division of Submission Support in the Office of Regulatory Programs, or ORP, Becky Nipper, Associate Director of Regulatory Programs and Guidance, or RPG in the OPEQ, Immediate Office OPEQ, the Office of Product Evaluation Quality, and Dr. Connie Soves, policy analyst also at RPG, so as we open up to our question and answer portion, please click the Raise Your Hand button, which should appear on the bottom of your Zoom screen.

I'll announce your name, invite you to ask your question. To do so, you'll need to unmute yourself when called and then ask the question. A few tips about asking questions, please ask only one question and try to keep it as short as possible. This will help us get to as many questions as we can. Also, please do not ask any questions about specific submissions.

For any specific submission questions, we ask that you consider submitting a Q submission or reaching out to the team offline. After you ask your question, please unmute yourself again. If you have more questions, no problems, just go ahead and raise your hand again, and go back in, and we'll circle back to you if we have time. Now as we wait for those questions to load in, I am going to start with one question that we received from the Division of Industry and Consumer Education in the last few weeks.

And this one will go addressed to Peter. In your presentation, you noted that you're aligning with the current De Novo practice despite all of the changes. So what is actually changing from the current process?

Peter Yang: Hi Joe, great question. So yeah, so you're sort of right that the vast majority of the time, it's actually business as usual. It's still the same regulatory standard. It's still the same timeline. It's still the same general review practices. The changes are really kind of all on the edges. The most meaningful change that I think most people will notice day-to-day is the new RTA checklist, the new refuse-to-accept checklist, which requires a lot of information which will be helpful to FDA in its review.

There are more items, and so please take a look at the guidance. You can put them up side-by-side and see what the differences are so that you can understand what FDA is requesting. A lot of De Novos already include a lot of the information required by the checklist anyway. And so for most De Novos, they may not actually notice a significant change. But overall, things are not changing in a big way. The key benefit for FDA is that the regulations formalize the process in a way that's not just implemented through guidance.

Joseph Tartal: OK, thank you, Peter. And our first live question of the day is from Carrie Long. I'm going to unmute you, Carrie, and then please ask your question. You're currently unmuted. Carrie, please unmute yourself and ask your question.

Carrie Long: Sorry, I was wondering about the links to the different documents. We can't access those on this PowerPoint. So are those going to be sent out to us afterwards?

Joseph Tartal: So the links that are found, we are not going to send the entire presentation out. But there will be a recording available. And I believe you'll be able to access those through the recording.

Carrie Long: OK, thank you.

Joseph Tartal: Our next question is from Allison. I'm going to unmute you, Allison. Please then unmute yourself and ask your question.

Allison Komiyama: Can you hear me?

Joseph Tartal: Yes, yes I can hear you.

Allison Komiyama: Thank you. Thank you, Peter. This is Allison Komiyama. I just had a quick question about submitting a De Novo for a class I or requesting a class I regulation. And you said that you'd have to demonstrate that the device can meet general controls. Does that mean that we still should submit all of the data to demonstrate that the device is safe and effective, but that we'd also be able to still demonstrate that you don't need special controls and that it would be acceptable to be a class I device?

Would you, and maybe a follow up question is, would you get kicked out of the-- or would you get refused if FDA didn't agree that you were potentially a class I device that you would be more eligible for class II?

Peter Yang: Sure, great question. So with respect to your first question, I think it's basically as you propose, right? So in order for FDA to make a classification decision, we have to determine that general or general and special controls can provide reasonable assurance of safety and effectiveness. So part of that is really understanding the benefits and risks of your device. And so you may need data that sort of outside of what you could describe, you could provide to demonstrate that you need general controls.

You might need to provide data to demonstrate the device actually has benefits for patients. And so we do need the information to make a decision to classify either as class I or class II. The question for us is really our general control sufficient to provide reasonable assurance given the data that you've provided? Or is it that we need specialized testing or other kinds of requirements for your device and other similar devices moving forward. And that sort of the question.

So in some cases where we classify devices as class I, we're saying we don't need additional special controls requiring testing specific kinds of testing or other kinds of requirements that it's sufficient for general controls to provide that assurance of safety and effectiveness. I think your other, question was about whether we disagree with the classification when we receive it.

So acceptance review is really predicated on whether the De Novo request is complete and whether it has the information necessary to begin review. It's not saying that we have to agree with your classification decision right away. We don't really make a classification decision as far as class I or class II until we've had a chance to review all of the information that you've provided.

So I don't think it's likely that we would say, "Hey, you think it's class I. We think it's class II. You need to restart." We would really try to resolve that during the course of review and sort of get more information from you regarding your position and why you think that class I or class II, class I or class II would be the best classification for your device.

Allison Komiyama: That's super helpful. Thank you. I have another question but I'll get back in line. Thanks.

Joseph Tartal: Thank you. So our next question is from Angelo. I'm unmuting you. Now, you need to unmute yourself and ask your question.

Angelo Gunasekera: Peter, I just wanted to know if the FDA is FDA allows the pre-submission now. I heard that they're not because of the COVID situation.

Peter Yang: Hi, it's a good question. So I think the questions about presubmissions. I will defer to Josh Nipper, the Division of Submission Support. I would say that's not a general case across all of the Center.

Josh Nipper: Hi, this is Josh Nipper. As Peter noted, I'm the Division Director for the Division of Submission Support. That question is largely off scope of this webinar. If you send an email to me. I think my contact is in here, joshua.nipper@fda.hhs.gov, we can address that. There are a few situations where we are still deferring review of presubs, but in general, we are reviewing them although our time frames are difficult. And where we're deferring review for a few weeks due to the COVID pandemic. But I can give you more information if you reach out directly.

Angelo Gunasekera: Thank you.

Joseph Tartal: Thank you, Angelo. Our next question is from Jason. I'm unmuting you, so please unmute yourself and ask your question.

Jason Lyon: Thank you. With a De Novo, my guess is that a clinical study is needed to support the device's safety and use. But once that De Novo has been classified, say it's a class II, do the devices that follow also require a clinical study? Or like most 510(k) class II devices, we present to FDA non-clinical data to demonstrate substantial equivalency? Thank you.

Peter Yang: Yeah sure that's a great question. So to answer your first question, it's not necessary that you provide clinical data to demonstrate the benefits of the device. There may be instances where you can provide animal data. For example, if you wanted to provide something like histopathology or other kinds of information that would be best obtained through an animal study. That may be what's necessary to demonstrate the benefits of the device.

So I don't necessarily want to speculate about any particular instance. But we don't require clinical data in order to-- as a matter of course to demonstrate that the benefits outweigh the risks. That said, yes, the majority of De Novo requests do contain clinical data. Then having said that, the question for FDA becomes in the least burdensome way what kinds of controls are needed to provide reasonable assurance of safety and effectiveness moving forward for future 510(k) devices.

And we've done it both ways depending on the particular indication or sorry, the intended use and the technology, there may be some instances where clinical data is the least burdensome way to provide reasonable safety and effectiveness in a 510(k) context to help demonstrate the device is as safe and effective as the original De Novo device. But there are also cases where clinical data may not be necessary moving forward.

And there are other ways to demonstrate substantial equivalence and provide that assurance of safety and effectiveness to where clinical data is not necessary for every 510(k). The last thing I want to say is in the 510(k) process, it is possible for FDA to request clinical data to support a particular change in indications. But again, that would be on a case by case basis depending on the particular change and the particular device. And so on.

Joseph Tartal: Did that answer your question, Jason?

Jason Lyon: Yes, but I hope we can distinguish between clinical and non-clinical. Because typically with a substantial equivalency, it's usually non-clinical data that's used to demonstrate substantial equivalency. Clinical data for me would be like animal study or human studies, things like that. Actually, I'm sorry,

take it back just human studies. So that's what I was referring to. But I believe for the most part you've answered my question, Mr. Yang. Thank you.

Joseph Tartal: OK, our next question is from KXL. I'm unmuting your mic. Please unmute yourself and ask your question.

Kevin: Right, sorry, this is Kevin. Hello?

Joseph Tartal: Yes, we can hear you.

Kevin: OK, great, sorry. So the question is we talk about the ability to do inspections. And obviously, the De Novo is a predicate for a 510(k). FDA doesn't inspect 510(k) manufacturers in the premarket. But very just for clarity's sake, the inspections that are done for the De Novo process and review may be done in the premarket. Is that correct?

Peter Yang: Yes, that's what we're saying is that for De Novo reviews, during our review, so that would be in the premarket phase, that we have the authority to inspect for reasons related to data integrity and then quality system regulation questions for novel critical or novel manufacturing processes.

Kevin: Right, all right, thank you. I'm going on mute now.

Joseph Tartal: Our next question is from Karin. Karin, I'm going to unmute. Please unmute yourself and ask your question.

Karin Hughes: Hi there. Thanks so much. That was really helpful. Quick question, does the submission need to follow the order of the content as specified in 860.220?

Peter Yang: No, I mean, obviously hopefully your table of contents is first, right? But as far as the other content and sort of the way in which you want to arrange it, I would say that the way to arrange it that best seems make sense for you and is helpful for you to explain your device, that's certainly fine. Our acceptance request is not checking or sorry, our acceptance review is not checking your specific order but checking to make sure that the content is there.

Karin Hughes: Perfect, I like your answer. Thank you.

Peter Yang: Sure.

Joseph Tartal: OK, our next question is from Joseph. Joseph, I'm muting your mic. Please unmute yourself and ask your question.

Joseph DeCroos: So my question has to do with marketing a De Novo device. So I know typically with the 510(k), we say things like cleared by the FDA. We're encouraged not to say things like approved by the FDA. I'm wondering if with the De Novo device if there's any specific verbiage that we're supposed to are not supposed to use.

Peter Yang: Hey, thanks for your question. We get this question occasionally. I guess the way the sort of most clearest way to say sort of your favorable decision there is that your De Novo request has been granted. Other terms you can use are you can say you've been granted marketing authorization. I think

if you have a particular question, I think you may be able to ask some of our media folks. And so we can get back to you with particular language.

You can also email me personally or the Division of Industry and Consumer Education if you're looking for the right language to use. I appreciate it's a little bit grammatically sort of challenging, but we wanted to differentiate what's rendered on a De Novo decision compared to approved PMAs or cleared 510(k)s so it would be granted De Novos.

Joseph DeCroos: That makes a lot of sense. Thank you.

Joseph Tartal: Our next question is from VFleck. I'm unmuting your mic. Please unmute yourself and ask your question.

VFleck: Hi there. Can you hear me?

Joseph Tartal: Yes.

VFleck: Great, so I also had a question about inspections. Just wondering if you can give an overview of how inspections are typically incorporated to the De Novo review process, specifically if you could talk about when sponsors are typically notified, when an inspection is required for the manufacturing when there's a manufacturing question.

Peter Yang: Sure, I guess I can't really point out a specific time point that we're going to request. We certainly don't have a specific requirement in our review processes that dictates by day such and such, we have to request. It's dependent on FDA review workload and when we can identify an issue that says that we need to look into this further. Obviously, the inspection process takes some time, and we need to be able to fold that into our decision making. And so it's our goal to identify those issues and begin work on those issues as expeditiously as possible.

I will just say that before the final rule is implemented, we're not going to inspect for that reason specifically. So I would say our processes around acquiring the sort of information and sort of working through that are still going to be new. But again, the overall sort of message that I would say is we're still-- we intend to do that as quickly as possible so that we can fold that into our review process and make a decision quickly.

VFleck: OK, thank you very much.

Josh Nipper: This is Josh Nipper. I'd like to jump in a little again. And Peter's answer was absolutely correct. I would also note if you have questions about the inspection, if you're using a novel manufacturing technique and novel sterilization technique, something new and different, these are great questions to explore with FDA in a presubmission. We never intend for this inspection to come as a surprise to you. So hopefully, if this inspection comes up during a De Novo review, you kind of saw it coming, and we're aware that this may be on the table.

And so if you have questions surrounding this, it's a great time before you submit your De Novo a couple of months before, put that out there and say, "Look, we have this novel manufacturing method. We want to know is this something that FDA is going to require inspection for." Because it gives us an advance warning as well that we can work with our colleagues in ORA in a non-COVID world which we

all hope we get to soon that we can then begin to reach out to our colleagues in ORA and say, "We have this coming down the line. We think it may need a pre-approval inspection." And hopefully we can expedite some of that timing.

But as Peter said, this is somewhat of a new process for us. And so when we come across these scenarios, we're going to have to explore that with the company a little bit.

Joseph Tartal: OK, thank you, Josh. We have time for one more question. Lucas, I'm going to unmute you. Please unmute yourself and ask your question.

Lucas Fernandez: Hi, this is Lucas Fernandez. My question was around the publication of De Novo decisions in particular. So if I have a second De Novo say going behind the now may seem be rendered invalid or where the first granted De Novo now becomes a likely predicate, what would be-- would that be FDA notifying the submitter or the sponsor of that second De Novo, or is that something with the sponsor themselves would request to pull back that De Novo and then convert to a 510(k)?

Peter Yang: Yeah, hey, that's a great question. So it's not-- it happens rarely, but it happens often enough to where we actually talk about this in our guidance document. So it may be the case where two De Novos are being reviewed at the same time and one of them gets granted before the other. In that case, the first De Novo is granted. The second De Novo becomes ineligible because the first De Novo now exists. Now there's a new regulation.

And so at that point, we will go to the second sponsor and offer an option. So either they can withdraw their De Novo request and begin preparing a 510(k) to demonstrate substantial equivalence to the recently granted De Novo device or their device will-- their De Novo request will be declined for reasons of ineligibility. Now in that instance, hopefully we've already had some interaction with the second De Novo sponsor.

So we've had a chance to talk about the file, had a chance to communicate some of our deficiencies. And so hopefully the subsequent 510(k) would be reviewed quickly. But that said, sort of depends on the timing of everything and that would be the options for the second De Novo once the first one has been granted.

Joseph Tartal: OK, does that answer your question?

Lucas Fernandez: Yes, thank you.

Joseph Tartal: OK, thank you. And I'm going to turn it over to Peter for his final thoughts before I conclude the program. So Peter?

Peter Yang: So thanks very much, everyone, for participating. If you have any questions, and I know somebody asked about the links, please feel free to search. If you just go to Google and you just pop in a search request for any of the terms that we talked about today, everything should be available there. Please email me or the Division of Industry Consumer Education if you have any questions, and hope to hear from you soon. Thanks.

Joseph Tartal: This concludes today's CDRH webinar. I'd like to thank our panelists Doctors Peter Yang and Connie Soves as well as Josh Nipper and Becky Nipper for the discussion about the De Novo

program, and our thanks to our audience for your participation and questions to the FDA panel. A recording of today's webinar presentation and transcript will be posted to CDRH Learn in a few weeks. Please visit CDRH Learn at the link shown on the final slide, www.fda.gov/training/cdrhlearn.

This topic will be placed under the De Novo section, which you can find under the category how to study and market your device. Here's a screenshot of where you can find the presentation. For additional questions about today's presentation, please email us at DICE@fda.hhs.gov. We appreciate your feedback about the CDRH webinar program series and encourage you to complete a brief survey which you may find at the link shown www.fda.gov/cdrhwebinar.

We also encourage you to attend future CDRH webinars. The link on the bottom of the slide provides a listing of all scheduled upcoming webinars. Again, thank you for joining us today. Take care and see you next time.

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