

**NWX-FDA OC**

**Moderator: Irene Aihie**  
**August 08, 2016**  
**1:00 pm ET**

Coordinator: Welcome and thank you for standing by. At this time, all lines are in a listen-only mode until the question and answer session. For today's call, we will not be taking questions from the chat box but from phone lines only.

If you'd like to ask a question at that time, you may do so by pressing Star then 1 and recording your first and last name. Today's call is being recorded. If you have any objections, you may disconnect at this time. I would now like to introduce your host for today's call, Ms. Irene Aihie. You may begin.

Irene Aihie: Thank you. Hello and welcome to today's FDA webinar. I am Irene Aihie of CDRH's Office of Communication and Education.

On June 20, 2016, the U.S. Food and Drug Administration published the final guidance Leveraging Existing Critical Data for Extrapolation to Pediatric Uses of Medical Devices providing a framework to consider extrapolating existing data to evaluate a devices performance in pediatric patients in premarket approval applications, PMAs, humanitarian device exemptions, HDEs, and De Novo requests.

This guidance facilitates continued efforts to address unmet medical device needs for pediatric patients. The focus of today's webinar is to share information and answer questions about the final guidance document.

Today's presenter is Dr. Vasum Peiris, Chief Medical Officer for the Pediatrics and Special populations, Special Populations from the Office of the Center's Director here in CDRH.

Following the presentation, we will open the lines for your questions related to topics in this final guidance only. Additionally, there are other center subject matter experts available to assist with the Q and A of our webinar. Now, I give you Vasum.

Dr. Vasum Peiris: Thank you very much. Thank you everybody for joining us today. As you can see, the title of our webinar is Leveraging Existing Clinical Data for Extrapolation of Pediatric Uses as Medical Devices.

My name is Vasum Peiris and I'm the Chief Medical Officer for Pediatrics and Special Populations with the Center for Device and Radiological Health at the FDA. Our webinar objectives today are basically three. We'd like to provide context for overview of the final guidance, describe the key changes from the draft guidance to the final guidance documents.

And at the end we'll have some time to answer any clarifying questions about the concepts in the final guidance. Let's go ahead and get started. The FDA, as I hope everyone realizes, dedicated to promoting timely access to safe and effective medical devices for all patients and we recognize the unique needs of pediatric patients.

Despite this understanding and recognition of the need, currently there are relatively few medical devices that have pediatric specific indications and labeling. The final guidance proposed a framework to leverage appropriate data for minimizing risk to pediatric patients while maximizing access to medical devices indicated for pediatric patients.

And we hope that this approach may stimulate growth in a number of devices indicated and labeled for pediatric patients.

We begin with a little bit of the regulatory background that gives us the authority to consider extrapolation basically titled three of the Food and Drug Administration Amendments Act which we levy and call FDAAA is the Pediatric Medical Device Safety and Improvement Act of 2007 and we tend to refer to this as PMDSIA.

So PMDSIA specifically authorize the use of adult data to demonstrate pediatric effectiveness.

The language in the legislation specifically reads if the course of the disease or condition and the effects of a device are sufficiently similar in adults and pediatric patients, the secretary may conclude that adult data may be used to support a determination of reasonable assurance of effectiveness in pediatric populations as appropriate.

In addition, CDRH believes that extrapolation for safety is also appropriate in certain circumstances. So basically, what do we mean by extrapolation? And I intend here to clarify how we are utilizing the term extrapolation in the document.

So in this guidance, extrapolation refers to the leveraging process or indication in a new pediatric patient population to be supported by the listing clinical data from studied patient populations.

So basically when existing data are relevant to a pediatric indication and determined to be valid scientific evidence, it may be appropriate to extrapolate such data for pediatric use.

One of the issues that seems to have a little bit of confusion and the exact definition of the pediatric age ranges, let me try to clarify that here.

So the age ranges for the pediatric subpopulations are as follows, for neonatal basically from birth to approximately one month of age, for infants greater than one month to two years of age, children greater than two to 12 years of age, and adolescents greater than 12 through 21 years of age.

And basically this is really saying that it's less than 22 years of age so up to but not including the 22nd birthday. Of note, there are other definitions of the pediatric age ranges which are used by other centers and other government agencies.

As many people may understand, there are challenges to actually developing pediatric indications for devices and utilizing pediatric patients within study populations. Some of those challenges are listed here.

Basically pediatric populations may be small and (unintelligible) scattered potential study populations (unintelligible). Enrollment and consent procedures may increase trial time. There are also increased, there are also increased variation to the physiology, (unintelligible) physiology, anatomy, and human factors as compared to adults.

And this challenge is development of appropriate technologies. Due to many of these challenges, adult devices tend to get used off label in pediatric patients and when adult devices are used off label in pediatric patients, it becomes difficult to clearly understand basically accurately evaluate the needs for pediatric patients.

And also becomes difficult to understand accurately what issues may mitigate safety and effectiveness in these devices that are being utilized off label in pediatrics.

So why should we consider extrapolation? When leveraging relevant critical data, when appropriate may lead to a few hopeful benefits. We believe that it will lead to more devices being granted marketing authorization for pediatric indications, it increases availability of medical devices with appropriate label, labeling to support safe and effective device use in pediatric patients.

We hope it will streamline the process for establishing pediatric intended use claim and will enhance to encourage pediatric device development programs. With this slide, I'd like to highlight a few of the key areas of the document itself.

And if you have the document with you, you can certainly refer back to this but any point the document is available both online and you can certainly print out a copy for yourself.

The document has a background section that goes into the regulatory history and it also discusses the purpose and potential benefits of extrapolation. The areas I'd like to direct your attention are the extrapolation decision process.

So figure one is a key aspect of the document and figure one provides the complete decision tree which we can utilize for considering extrapolation decisions. The document also discusses full versus partial extrapolation and also discusses extrapolation for effectiveness versus safety.

In addition, the appendix of the document is a great reference and gives examples of statistical methodology for extrapolation. The appendix specifically has a section that discusses potential statistical methods and also goes through six hypothetical and one actual example of extrapolation.

What are the objectives of the guidance? Basically, they are as we have indicated here, we want to increase the availability of safe and effective pediatric devices by providing a road map for leveraging relevant existing clinical data for use in premarket approval applications or PMAs, humanitarian device exemptions, and De Novo requests.

We want to explain the circumstances in which the FDA believes it may be appropriate to leverage existing clinical data to support pediatric device indications and labeling.

We'd like to outline the approach FDA uses to determine whether extrapolation's appropriate and if so to what extent the data can be leveraged. And we want to describe suggested statistical methodology that may be used to leverage the data in a way that increases precision for pediatric infants.

The guiding principles of the document. and here we'd like to just discuss what are the issues that really, that we have used to help guide our discussions and conceptual understanding of extrapolation fairly and responsibly serving the needs of pediatric patients is key and we're specifically looking to serve

those needs for devices of appropriate labeling to support safe and effective pediatric use.

In addition, the guidance does not change what we believe to be the threshold for approval or the need for valid scientific evidence. The appropriateness of extrapolation is also considered on a case by case basis and is guided by the decision tree that are referred to in figure one and we're considering these separately for both effectiveness and safety.

What determined the appropriateness of extrapolation? We consider three key factors.

First, similarity of existing adult response data and/or population characteristics to the intended pediatrics of subpopulation, two, the quality of the data, basically (unintelligible) design, data collection, and measurements, and three, fair and responsible support of a reasonable assurance of safety and effectiveness or probably benefit for HDEs.

And once again, valid scientific evidence does not change when this should, and the data should provide a support via valid scientific evidence. With this slide I'd like to highlight once again the decision tree which is again, I'll reference in figure one, the decision tree goes through three broad categories of consideration.

One is the relevance of the data. Basically, does the disease or condition occur in a pediatric population, subpopulation and are the endpoints in the datasets relevant to the intended pediatric population or subpopulation?

We also consider similarity of response to an intervention with respect to the device characteristics, the disease characteristics, and the population characteristics.

And again, the quality of the data and we're considering quality of the data, the question is the adult or other population data a sufficient quality to demonstrate safety and effectiveness in pediatric populations or subpopulations? And if not, is the data a sufficient quality for partial extrapolation?

With respect to full and partial extrapolation, full extrapolation basically means that existing clinical data are used directly such as complete substitute for prospective pediatric clinical data.

Partial extrapolation is that existing data are combined via a statistical model with pediatric data sources or prospective pediatric clinical data, so partial extrapolation permits utilization of existing clinical data to support demonstration of device safety or effectiveness for use in pediatric patients with the expectation that some pediatric data are necessary.

And if not appropriate or sufficient to meet the threshold of valid scientific evidence, data will not be extrapolated. A key message that we'd like to get across is that extrapolation does not imply approval.

So conclusion that extrapolated data may be used does not necessarily mean that the data will support an approval decision. If extrapolation is deemed appropriate, the data would be considered in conjunction with the totality of evidence to either support or not support the reasonable assurance of safety and effectiveness or probable benefit.

So our next section of the webinar will include some of the key changes with respect to from the draft guidance to this final guidance. So the final guidance clarifies and explains the following, the guidance applies specifically to PMAs, HDEs, and now De Novo requests for pediatric indications thought.

As we noted earlier, PMDSIA states that extrapolated data may be used to support a reasonable assurance of effectiveness, extrapolation for safety may be appropriate in some circumstances.

PMAs and De Novo requests both require a demonstration of a reasonable assurance of safety and effectiveness. HDEs require a demonstration of safety and probable benefits. Extrapolated data may be particularly useful in HDE given the (unintelligible) of a disease or condition that's being addressed.

And one of the key takeaway points from the information presented in this slide is that based off these issues for review of data that provides reasonable assurance of effectiveness and safety, the guidance does not currently address 510Ks and does not apply to the 510K process.

Another change from the draft guidance to the final guidance it clarifies the concept of borrowing strength so quantitative information provided by existing adult or other population data may be incorporated in one of two ways, either as a substitute for any potential pediatric data or as a supplement to new pediatric data considered in the context of statistical model.

It also clarifies how to determine similarity in device effects. Both the direction and magnitude of the device effects should be considered so by direction of a device effect, we mean that if the device has a benefit for adults, it should also have a benefit for pediatrics.

The magnitude of benefits should also be similar between the populations. So our next steps, with respect to implementation. CDRH will use pediatric expertise in the evaluation of any application which extrapolation's considered and we're currently in the process of developing the PED's team which I know you all think is an exceptional acronym.

It stands for Pediatric Extrapolation for Devices team and this will be a centralized group with pediatric expertise. They will be available for consultation regarding extrapolation and we believe that this team will enhance consistency in standardization with respect to extrapolation decisions.

In conclusion, as I mentioned earlier, despite a recognized need, relatively few medical devices have pediatrics specific indications and labeling. The guidance proposes the framework for leveraging existing data to augment availability of medical devices indicated and labeled for pediatric patients.

The guidance provides clarify and predictability for device sponsors and enhances consistency within FDA regarding decisions involving the extrapolation. I want to thank you very much for your time and we can now open up the session for questions.

Coordinator: We would now like to begin the formal question and answer session of the call. If you'd like to ask a question, please press Star then 1 and record your first and last name. Again, that's Star then 1 and record your first and last name. If you'd like to withdraw your question, you may press Star, then 2. One moment for the first question, please.

Dr. Vasum Peiris: I'm assuming now that we don't have any questions requests yet, that means that our, oh, looks like we do have one.

Coordinator: We do have questions. One moment while I gather the information. First question comes from (Tara Beteriche). Your line is open.

(Tara Beteriche): Hi, Dr. Peiris. (Tara Beteriche) with (unintelligible). I want to thank you for issuing the final guidance. We appreciate the changes that were made to the guidance. You referenced the fact that the guidance does not cover 510Ks, do you have the, have you started or do you have the intention of developing guidance for extrapolation of adult data to PEDs for 510Ks?

Dr. Vasum Peiris: Thank you, (Tara). How are you? Thanks for the question. There obviously, as you mentioned, we appreciate the support in terms of completing the guidance but a great deal of people have worked on this so I definitely want to recognize all the people that have done work.

With respect to your question specifically as I mentioned, the guidance document does not address 510Ks specifically. We are willing to consider extrapolation requests in all forms but the guidance document itself does not address 510Ks.

(Tara Beteriche): Thank you for that explanation.

Dr. Vasum Peiris: Thank you.

Irene Aihie: We'll take our next question.

Coordinator: Next questions comes from (Jen McDerma). Your line is open.

(Jen McDerma): Hi, thank you for that last question. It was actually kind of the question that I wanted to ask but in addition to that, if the device is eligible for 510K and you are seeking to obtain a pediatric clearance, what does FDA recommend that a

manufacture do to establish extrapolation of data that would, that would support a 510K?

Dr. Vasum Peiris: Thank you for your question. We definitely want to keep the questions specific to clarifying issues with respect to the guidance document itself but I would suggest that if you have any concerns of that nature that developing - contacting the FDA and speaking with potentially a presubmission team would be beneficial.

And earlier the contact the better off you'll be with respect to clarity of information that will hopefully make your pathway towards approval efficient as possible.

(Jen McDerma): Okay thank you.

Dr. Vasum Peiris: Thank you.

(Jen McDerma): Yes.

Coordinator: Next question comes from (unintelligible) (Kim).

(Kim): Hi, Dr. Peiris, Thanks very much for holding this conference and I certainly want to applaud FDA for leading guidance on the, on this statement. Perhaps this may not be the best venue for this question but perhaps some guidance along these lines would be nice.

You know, device studies in pediatric patients are extraordinarily difficult to pursue. These are where we want to get direct pediatric data from and mostly because coverage for these procedures is based on state Medicaid agencies.

What does FDA, how does FDA view and suggest ways to be able to incorporate patients from a Medicaid perspective based on these coverage decisions? Is this something that needs to come through CMS or state regulatory agencies?

Just lastly, in the realm of pediatric chemotherapeutic trials, all states have agreed that they would, that state Medicaid would cover those kinds of research studies but device trials are specifically exempt in most states.

Dr. Vasum Peiris: I'm not sure I follow that one through.

Coordinator: Please continue to stand by.

Irene Aihie: We apologize, we had some technical difficulty. I think Vasum is going to go ahead and repeat his answer for the last caller.

Dr. Vasum Peiris: This is directed to the question that you had asked. This is my second attempt at this response (unintelligible) would either your more than welcome to reach out to me directly or you can actually reach out to DICE, the Division of Industry and Consumer Education and we, they can direct your questions appropriately (unintelligible). Thank you.

Irene Aihie: We'll take our next question.

Coordinator: Next question is (Dave Angle). Your line is open.

(Dave Angle): My question had to do with extrapolation of data from the other end of the curve. Neonatal data is very similar in some ways to infants so morphology and physiology change at about five years of age so the PEDs become more

adult like after that but at the early stages, they're more like neonates. So neonatal data be extrapolated for the infant category of PEDs.

Dr. Vasum Peiris: Thank you for your question, (Dave). You bring up a very good point with respect to the changes and development perspective to physiology from...

(Dave Angle): Sorry, we're having trouble hearing you.

Dr. Vasum Peiris: Can you hear me now?

(Dave Angle): Yes.

Dr. Vasum Peiris: Great. So you bring up a very important point with respect to the changes and physiology between a neonate and an infant. There are extreme variations with respect to critically neonates versus neonates that have gone through a full term gestation that has been healthy and that are developing as we consider quote on quote normally.

So these types of extrapolation quests will likely have to be considered based on as we've mentioned, a case by case basis with respect to understanding the distinctions and transition of physiology.

(Dave Angle): Would you accept it? Case by case?

Dr. Vasum Peiris: Sorry, could you repeat that again?

(Dave Angle): Could you accept it by cases by case? Is that what you're saying?

Dr. Vasum Peiris: Yes we're very willing to consider a case by case basis with, for extrapolation.

(Dave Angle): Thank you.

Dr. Vasum Peiris: Thank you.

Irene Aihie: We'll take our next question.

Coordinator: Next question comes from (Cindy).

(Cindy): Hello.

Dr. Vasum Peiris: Hi, (Cindy).

(Cindy): Hi. I was just wondering if you could help me by clarifying the neonate. Is it, when you say from birth, do you mean gestational age too, so preemies would be included in that group?

Dr. Vasum Peiris: Yes. So, and that's why the definition is basically from birth and as you can imagine and you may be very well aware, neonates that are born at let's say, 30 weeks gestation may have very different physiologies than a neonate that is born at 40 weeks gestation.

(Cindy): Correct, okay. Thank you very much.

Dr. Vasum Peiris: You're welcome. Thanks for the question.

Coordinator: Again, if you'd like to ask a question, please press Star than 1 and record your first and last name. Next question comes from (Mirage Patel). Your line is open.

(Mirage Patel): Yes, how does the FDA and HHS get results from the medical devices that are going on here and there? This morning, I was near my kitchen and felt a medical devices testing me in my cardiovascular area. Where is all this data going to to help human services and what's the purpose of it?

Dr. Vasum Peiris: Thank you for your question, (Mirage). I can't speak specifically to your request but again, I want to make sure that your concerns are addressed and I can direct you once again to DICE, the Division of Industry and Consumer Education and they'd be happy to help direct your question...

(Mirage Patel): Okay.

Dr. Vasum Peiris: ...appropriately and get that information for you.

(Mirage Patel): Thank you.

Dr. Vasum Peiris: Thank you.

Coordinator: Again, if you'd like to ask a question, please press Star then 1 and record your first and last name. There are no other questions. I would like to turn the call back over to Irene Aihie.

Irene Aihie: Thank you. This is Irene Aihie. We appreciate your participation and thoughtful questions. Today's webinar and transcript will be available on the CDRH Learn website at [fda.gov/training/cdrhlearn](http://fda.gov/training/cdrhlearn) by Tuesday, August 16.

If you have additional questions about the final guidance, please use the contact information provided at the end of the slide presentation. As always, we do appreciate your feedback. Again, thank you for participating and this concludes today's webinar.

Coordinator: This concludes today's call. You may disconnect at this time.

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