

**FDA Webinar: Benefit-Risk Factors to Consider When Determining Substantial
Equivalence in Premarket Notifications (510(k)) with Different
Technological Characteristics: Final Guidance**

Moderator: Irene Aihie

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Coordinator: Welcome and thank you for standing by. All participants will be in listen-only mode until the question-and-answer session. At that time please press star followed by the number 1 to ask a question.

Today's conference is being recorded. If you have any objections, you may disconnect at this time. I'd now like to turn the call over to your host, Irene Aihie. You may begin.

Irene Aihie: Hello and welcome to today's FDA webinar. I am Irene Aihie, of CDRH's Office of Communication and Education. On September 25th, the FDA issued the Final Guidance, Benefit-Risk Factors to Consider When Determining Substantial Equivalence in Premarket Notifications (510(k)) with Different Technological Characteristics. The goal of the guidance document is highlight factors the FDA considers when evaluating benefits and risks of a new device compared to a predicate device during a 510(k) review when the FDA has determined that the intended use of the device is the same, but there are different technological characteristics.

Today, Ifeanyi Uwemedimo, Biomedical Engineer, here in CDRH, will present an overview of the guidance document. Following the presentation, we will open the line for your questions related to information provided during the presentation. Additionally, there are other Center subject matter experts here with us today to assist with the Q&A portion of our webinar. Now, I give you Ifeanyi...

Ifeanyi Uwemedimo: Good afternoon. Thank you Irene for the introduction. As Irene noted, my name is Ifeanyi Uwemedimo and thank you all for attending today's Webinar on the 510(k) benefit-risk guidance.

The official guidance title is Benefit Risk Factors to Consider When Determining Substantial Equivalence in Premarket Notifications with Different Technological Characteristics.

The objective of today's training is to understand the purpose of the guidance and the policy specified within the guidance. We also want FDA staff and industry to understand when a benefit risk assessment is recommended in a 510(k), how the guidance can be applied and factors to take into consideration when conducting a benefit-risk assessment.

I will also touch-on who performs a benefit-risk assessment. As Irene noted we have saved some time at the end for questions and during that time we will address any questions you have. A little bit of background, the draft guidance was issued in July of 2014. At that time we received 96 comments from nine different groups.

We received a handful of very similar comments and based on the feedback, the main revisions to the draft guidance fell into one of the three categories.

Firstly, we clarified that the guidance does not change the current 510(k) review process or SE standard.

We also clarified that benefit-risk assessment does not imply submission of clinical data. This was a fairly common misunderstanding based on the feedback we received. Lastly, we clarified what is expected in a 510(k) benefit-risk assessment.

As a reminder, a guidance document is not binding to FDA or the public. The draft guidance is intended for input and not implementation whereas the final guidance represents the agency's current thinking on a specific topic. If a submitter chooses to use an alternative approach than the policy specified in a guidance, this is okay if it's supported with appropriate scientific justification.

So, the final 510(k) benefit-risk guidance outlines the policy for evaluating substantial equivalence in a 510(k) when the benefit-risk profile of a new device is different from that of a predicate device based on the performance data.

The guidance also specifies two situations when a benefit-risk assessment is recommended. The first situation is when there is an increase in risk along with an increase or equivalent benefit. The second scenario is when there is a decrease in benefit along with a decrease or equivalent risk when comparing a new device to a predicate device.

There is also a section dedicated to performance data. As you know, the probable benefits and risk of a device are based on valid scientific evidence. Valid scientific evidence can include both non-clinical and clinical data. Section 4 of the guidance touches-on factors to be taken into consideration

when conducting a benefit-risk assessment. We will touch on these factors later in today's training.

The last section of the guidance includes example scenarios which walk through whether a benefit-risk assessment is recommended. If it is recommended, we address factors that were taken into consideration and how the assessment was used to inform the SE decision.

It is important to note that this guidance does not change the 510(k) premarket review standard nor does it create extra burden for submitters to provide additional performance data or information we would not typically request for in a 510(k).

The 510(k) benefit-risk guidance serves as an aid. It is intended to provide guidance specifically in situations when the benefit-risk profile of a new device is different from that of a predicate device. The guidance also provides additional clarification on factors FDA takes into consideration when conducting a benefit-risk assessment.

Like all guidances, it is intended to improve predictability, consistency, and transparency.

So while a benefit-risk assessment is the basis for premarket review, it is important to understand that the benefit-risk framework for 510(k)s is fundamentally different from that of PMAs, De Novos and IDEs in the sense that for 510(k)s you're comparing the benefit-risk profile of a new device to that of a predicate device in order to determine substantial equivalence.

Whereas for PMAs and De Novos, it is not a comparison. It is an independent assessment of a device's benefit-risk profile. For IDEs it is also an independent assessment; however, we are willing to tolerate greater levels of

uncertainty prior to a clinical study that will help us garner more information on the benefit-risk profile of a new device.

Irrespective of the submission type, the probable benefits and risk of a device are based on valid scientific evidence. As I previously mentioned, valid scientific evidence can include both non-clinical and clinical data. I would also like to note that we do not typically see clinical data in 510(k) submissions. On average we see clinical data in less than 10% of 510(k) submissions we receive annually.

Of course FDA understands that there are situations when the benefit-risk profile of a new device is different from that of a predicate device; however, these differences do not automatically result in an NSE decision.

What FDA does, is we determine whether the differences impacts SE. As I previously mentioned, the guidance is intended to provide direction in situations when the benefit-risk profile of a new device is different from that of a predicate device. The guidance also specifies two situations when a benefit-risk assessment is recommended.

If we look at Quadrant 1 in the table on the right, a benefit-risk assessment is recommended in a situation where there is an increase in risk along with an increased or equivalent benefit. For the second scenario in Quadrant 3, benefit-risk assessment is also recommended when there is a decrease in benefit along with a decrease or equivalent risk.

If we look at the scenario in Quadrant 2 where there is an increase or equivalent benefit along with an increase or equivalent risk, this scenario is fairly clear cut and would likely result in an SE decision. If we look at the scenario in Quadrant 4 where there is an increased new risk along with an

increase in benefit, this is also fairly clear-cut and would likely result in an NSE decision.

So a benefit-risk assessment is recommended in a situation when the benefit-risk profile comparison falls under Quadrants 1 or 3 and if one is unsure whether the new device is substantially equivalent to a predicate device based on the differences in the benefit-risk profile.

The guidance includes a reference table that serves as a guide for when benefit-risk assessment is recommended. However, this table should not be used in isolation and should be used with the guiding principles outlined in the rest of the document. As I previously mentioned, there are a few situations when benefit-risk assessment is recommended.

For the scenario in Quadrant 1 where there is an increase in risk along with an increase or equivalent benefit, it is important to note that FDA will generally not deem a new device SE if there is an increase in risk that cannot be appropriately mitigated and if the increase in risk is not accompanied with an increase in benefit.

In the second scenario in Quadrant 3 where there is decrease in benefit and a decrease or equivalent risk, FDA will likely not find a new device substantially equivalent to the predicate if there is a decrease in benefit that is not accompanied with a decrease in risk and if the benefit-risk assessment confirms that the new device is not as safe and as effective as the predicate device.

So when can you conduct a benefit-risk assessment? Well, a benefit-risk assessment can be conducted after you have evaluated the performance data and determined that the benefit-risk profile comparison falls under Quadrants

1 or 3. For this guidance we leveraged the 510(k) decision-making flowchart and pointed to the step in the decision-making process when a benefit-risk assessment may be helpful.

We could not fit the whole flow chart on this slide without compromising readability, so in summary, a benefit-risk assessment is conducted after it is determined that the predicate device is legally marketed, the intended use of the new and predicate devices are the same and if there are differences in technological characteristics, the differences do not raise new questions of safety and effectiveness. Therefore, a benefit-risk assessment is conducted after decision 5A but before decision 5B.

When thinking about the effect of a device on patient's health and/or clinical management, FDA considers several factors when evaluating the extent of probable benefit.

These factors include the type of benefit which is often predefined by endpoints, the magnitude of the benefit which is assessed based on these predefined endpoints and the probability that the patient will experience one or more benefits. FDA also considers whether there is variability and benefit within sub-populations in a group.

We also consider the duration of effect. This also helps us to determine whether use of the device or intervention is worth it. Likewise, FDA considers several factors when evaluating the extent of probable risk including the type, severity, rate, and probability of harmful events.

In other words what is the risk, how bad is it, how frequently does it occur, and what are the chances that it will occur? FDA also considers the probability that the patient will experience one or more harmful events and if

the device is a diagnostic device, we consider the risk from false positive or false negative results. In other words, what are the chances that a patient will accidentally receive or not receive a treatment that they need?

This slide shows the additional factors that FDA takes into consideration when conducting a benefit-risk assessment. Section 4 of the guidance touches on each of these factors in detail.

For this training, I will touch-on each factor very briefly. Uncertainty in a benefit or risk can be due to the quality or lack of quality of valid scientific evidence. A number of factors can affect the degree of uncertainty including things such as poor bench testing, small sample size, inadequate data analysis or poor study design.

FDA also considers the disease condition. In other words how does the disease manifest within a patient, what are the symptoms and how is the disease currently treated?

We also value patient perspective because we understand that the way a patient perceives a benefit or risk might be different to that of a scientist or clinician. Additionally, there are patients who are willing to tolerate more risk in order to gain the benefits of a device.

FDA also considers the benefit for the healthcare professional, patient or caregiver because we recognize that there are tools that could positively affect or improve patient management; and in a situation where there's an increase in risk when comparing a new device to that of a predicate device, risk mitigation strategies could help to minimize the probability or severity of a harmful event.

Post-market data is also important because it could help to provide understanding of the benefits and risks of similar devices and this information can be leveraged when conducting a benefit-risk assessment of a new device.

So who performs a benefit-risk assessment?

Well, if a benefit-risk profile comparison fits under Quadrants 1 or 3, the submitter can include a benefit-risk assessment in a 510(k); however, it is not required. If the lead reviewer determines that the benefit-risk profile comparison fits under Quadrants 1 or 3, the lead reviewer performs the benefit-risk assessment.

And if there isn't sufficient information in the submission to complete the assessment, the lead reviewer can request for additional information from the submitter to help complete the assessment.

As I previously mentioned, if there isn't sufficient information in the submission, FDA can request for additional information to help complete a benefit-risk assessment.

This is an example deficiency FDA could issue if additional information is needed. The deficiency request for a summary of the benefits and risks, any additional factors such as risk mitigation or post-marketing data that was taken into consideration.

In Part D we request for a conclusion on whether the benefits outweigh the risks. I also want to note that if a benefit-risk assessment was used to support substantial equivalence, a summary of the benefit-risk assessment should be included in the 510(k) summary.

In the next few slides, we will go through two example scenarios where a benefit-risk assessment is recommended. In this first scenario we have the

manufacturer of a condom, fabricated from synthetic material and the submitter is claiming SE to a natural rubber latex condom.

The only technological difference between both devices is the material; however, there was concern that the new material may not perform as well as the natural rubber latex and could result in breakage or slippage during sexual intercourse.

To assess these risks, the submitter performed a clinical study and assessed breakage and slippage as endpoints. The primary endpoints were met; however, the slippage rate for the synthetic condom was slightly higher than that of natural rubber latex condoms.

When we conduct a benefit-risk assessment we assess the overall benefits and overall risks based on the performance data. The benefit in this situation is that the new device provides another option for contraception and prophylactic particularly for people with an allergy to natural rubber latex.

The risk is that there is a slight increase in the slippage in comparison to that of natural rubber latex condoms which could result in increase of undesired pregnancies or STIs. When we consider additional factors, the submitter included a warning label stating that the device should only be used if the user has an allergy to natural rubber latex.

For the 510(k) analysis we consider the benefit-risk assessment. We acknowledge the benefit, in this case the device provided a form of contraception for people with an allergy to natural rubber latex.

However, the clinical study showed an increase in slippage rate in comparison to that of the predicate device; however, this risk was partially mitigated with

inclusion of warnings in the labeling so because the increase in risk was partially mitigated and because the increase in risk was also accompanied with an increase in benefit, the new device would likely be found substantially equivalent.

For this second example we have a laser therapy device for treatment of toenail fungus. This new device uses a different wavelength than the predicate device. The wavelength in the new device produces different photobiological effects in comparison to the predicate device.

It also has a constant energy delivery sequence whereas the new device has a pulsing sequence. A little bit of background for treatment of toenail fungus. There are two mechanisms of action. One is photobiological whereby the laser interacts with the chromophores within a fungal cell resulting cell death.

The second mechanism is a thermal effect on fungal cells where the cells are exposed to temperatures that result in tissue coagulation or vaporization. Due to the technological differences, the submitter conducted a clinical study comparing the new device to the predicate device.

The device would have equivalent benefit if it had a comparable responder rate to that of the predicate device so a responder is a subject whose toenail is effectively treated according to predefined success criteria.

The results of the clinical study showed that the clinical rate was lower in the group treated with the new device; however, due to the low power level the new device poses a lower risk in comparison to that of the predicate device.

So as we assess both the benefits and risks in comparison to the predicate device, for the benefits the new device offers an alternative treatment option;

however, the clinical study showed a lower responder rate. For the risk the lower power level for the new device offers minimal side effects when comparing the new device to the predicate device.

We took two additional factors into consideration: uncertainty and risk mitigation. There were significant data inconsistencies based on the data provided which resulted in a high degree of uncertainty. For risk mitigation we acknowledged that the laser safety protective glasses can be used to prevent accidental eye damage.

For the SE analysis we acknowledged that the clinical data showed that the new device had a lower responder rate. Although the new device imparts less risk due to the lower power level, the benefit was considerably smaller. Considering the high degree of uncertainty and small benefits observed, the new device would likely be found NSE based on lack of adequate performance data.

I do want to note that while the examples included in this training require clinical data, there are additional examples in the guidance where a benefit-risk assessment was conducted without the need for clinical data.

Considering the objectives of this training, there are three take-home messages. Firstly, FDA has released the final 510(k) benefit-risk guidance that serves as an aid when evaluating the benefit-risk profile of a new device especially in situations where there are differences in the benefit-risk profile of a new device in comparison to a predicate device.

Secondly, the guidance also specifies two scenarios where a benefit-risk assessment is recommended. Lastly, FDA understands that the benefit-risk profile of a new device does not have to be identical to that of a predicate

device and in situations where there are differences, FDA assesses how the differences impact substantial equivalence.

The benefit-risk assessment is not the final decision, but it's used to inform the final decision. This slide includes a link to the final 510(k) benefit-risk guidance. It also includes a link to existing guidance documents referenced in the subject guidance. I won't go through the list but the links on the slide are applicable.

Thank you all for calling-in to today's Webinar. We understand that this is a new policy so if you have any questions pertaining to the policy discussed today, please feel free to e-mail 510(k) staff. We check our mailbox between 8:00 to 4:00 pm during the weekdays and if you have any general questions, please feel free to e-mail DICE.

Thank you all for attending once again and we are ready to address any questions you have at this time.

Coordinator: Thank you and at this time to ask your question, please press star then 1. Please unmute your phone and record your name clearly at the prompt. To withdraw your request, please press star 2. Once again please press star 1 at this time to ask your question. One moment, please, for the first question.

Ifeanyi Uwemedimo: So while the questions are being queued, one common question we have received is does this policy change the NSE decision process? The answer is no. Benefit-risk assessment is used to inform the final decision. It is not the final decision nor does it change the final decision. Another question is what if you're unsure whether you need to include a benefit-risk assessment?

As we've previously mentioned a submitter can choose to include a benefit-risk assessment but it's not required and if you are unsure, we recommend referencing Table 1 in the guidance to determine whether the profile comparison fits into one of the quadrants and if you're still unsure, again you can always contact 510(k) staff.

Irene Aihie: Operator, we can take our first question.

Coordinator: Thank you. The first question is from (Ann Leonard). Your line is open.

(Ann Leonard): Yes, hi. I just wanted to ask then whether one would expect to see going forward that there would always be a risk-benefit sort of evaluation or conclusion in all of the 510(k) summaries, either whether they're produced by the sponsor or whether it's the work of the reviewer? Will either 510(k) now have a risk-benefit evaluation either summary or conclusion?

Ifeanyi Uwemedimo: So we're not expecting to see a benefit-risk assessment for all 510(k)s. Again the guidance does outline the two scenarios where a benefit-risk assessment is recommended and we anticipate that the chances of actually including a benefit-risk assessment will be fairly slim and again as we mentioned during the training, the submitter is not really required to include a benefit-risk assessment; however, you do have the option.

But in a situation where the lead reviewer determines that the benefit-risk profile comparison falls into either Quadrants 1 or 3, the lead reviewer is expected to complete a benefit-risk assessment.

(Ann Leonard): Okay, thank you.

Coordinator: The next question is from (Almda) and please state your company name when presenting your question, your line is open.

(Almda): Hi, hello, I'm calling from (grateful diagnostic solutions). My question is about the situation when the new device and the predicate device have the same technological characteristics as a predicate so you this case assume we don't need do this benefit and risk analysis?

And related question is like the (venme) if they have the same technological characteristics there is no further like benefit or risk ratio, use this situation?

Ifeanyi Uwemedimo: So I'll attempt to address your question and you can let me know whether I addressed it appropriately or not so a benefit-risk assessment is conducted after you've provided your performance data and you've determined that your benefit-risk profile comparison falls into one of the two quadrants that we previously mentioned.

In that case that's when we will expect to see a benefit-risk assessment; however, if it has the same technological characteristics and there isn't any substantial difference in the benefit-risk profile comparison, then we would not expect to see a benefit-risk assessment. Does that address your question?

(Almda): Yes and okay, maybe you can show me the slide. Yes, I was a little bit overlooked that.

Ifeanyi Uwemedimo: So before you even consider conducting a benefit-risk assessment, you already identify whether there is differences in technological characteristics or not and if there are differences, you have to first confirm that they do not raise any questions of safety and effectiveness. Again the benefit-risk assessment is only conducted after you've evaluated the performance data.

(Almda): Yes, my follow-up, if I remember that I see regulating correctly, when you have the same intended use and the same technological characteristics, you already have the substantial equivalent. Only when the technological characteristics are different you need to assess why they have I would say any effect on the safety and effectiveness.

So based on your FDA regulation, if they have the same technological characteristics or they have what substantial equivalence so in this case I shouldn't, you know, do the benefit and risk evaluation because it's not necessary.

Ifeanyi Uwemedimo: Correct.

(Almda): Okay, so does that mean that applied to the difference in the technological characteristics situation, you mean?

Ifeanyi Uwemedimo: I'm sorry, can you repeat that question?

(Almda): Okay, so I kind of assume this guidance mainly applies to when there is a difference in technological characteristics.

Ifeanyi Uwemedimo: Yes.

(Almda): Yes, okay. Okay, thank you.

Ifeanyi Uwemedimo: Thank you.

(Almda): No but when they have the same characteristics ...

Coordinator: The next question is from Adrienne Lenz. Your line is open and please state your company.

Adrienne Lenz: Hello, this is Adrienne Lenz with Hyman, Phelps & McNamara. My question is how will you handle situations where there's (unintelligible) information available regarding a predicate device, for example that the predicate was cleared under a previous guidance document where FDA may not have considered risks that they would be looking at today for a new device?

Ifeanyi Uwemedimo: That is a good question Adrienne. Can you give us a second to discuss it briefly?

Adrienne Lenz: Sure.

Ifeanyi Uwemedimo: So I just want to note that with use of the guidance our standard hasn't changed and we'll still consider the factors that we've outlined in the guidance.

((Crosstalk))

Adrienne Lenz: Yes, I just wasn't sure if there was more, thank you.

Ifeanyi Uwemedimo: And of course we'll handle each situation on a case-by-case basis but I think the important point that we are trying to make it that the standard has not - the standards for 510(k) - has not changed.

Irene Aihie: Okay, we'll take our next question.

Coordinator: Next question from Mark DuVal and please state your company.

Mark DuVal: Yes, Mark DuVal, DuVal and Associates here in Minneapolis. Just a question. We filed a docket submission on risk-benefit in 510(k)s two-three years ago, I can't remember now and challenging the agency's thinking on this that the Agency seemed to be, in our viewpoint, sort of legislating new requirements into the 510(k) program that really don't have its foundation in the statutes or the regulations.

So you shouldn't as a 510(k) device inherit the underlying regulatory presumptions that the device has already established safety and effectiveness and we shouldn't have to revisit that or a clinical utility and yet that sort of seems to be what we're doing here in a risk-benefit analysis.

I think I understand where the agency's trying to go with this but I'm not sure I think by doing this we're sort of emasculating the 510(k) program and if we want to change it, that's fine but we need to go to Congress to do it and I'm just wondering how you got there and how you believe that this is not tantamount to a legislative or regulatory change without either a statute or promulgating a new regulation.

Ifeanyi Uwemedimo: So we're not changing the 510(k) statute or regulation and I think the way we really want you to receive or understand this guidance is that it really serves as a structured tool when you're having a hard time reaching a final decision based on the performance data.

Mark DuVal: But can't we always punt to the performance data anyway and if it's really that different of a device, the outlet then would be I guess the De Novo program but the quantum and the quality of the data is one thing to request but to sort of fundamentally structure or build into the 510(k) program risk-benefit is just it seems to me this sort of mindless escalation of new requirements that really don't have any lineage in the statute or the regulation.

It's just kind of maybe a convenience for the agency put its mind around how it looks at things but now there's a layer added-on for industry to have to now do risk-benefit analyses whenever it's so deemed by the agency. Now they might be few and far between in the beginning but it might be commonplace five years from now.

((Crosstalk))

Woman: Hi, this is Angie Krueger. I think I would (enter) that by saying that the statutory and regulatory basis for the guidance is outlined in the guidance and we believe that the policy is squarely within the regulatory authority that we have so we're not changing the standard as Ifeanyi has noted and we also believe that it's built into the decision-making process in the regulatory approach that we take.

So I'd refer you to the regulatory section and background in the guidance to outline our thinking on that particular issue.

Mark DuVal: Good, we'll do that, thank you.

Coordinator: Next question is from Abdel Halim. Your line is open and please state your company.

Abdel Halim: Sure, Biomarkers and Diagnostics Consulting so my question is related to technological characteristics. Do you consider the analytics performance specifications or the mechanism of action (unintelligible) IVD or both?

For example, can next-generation sequencing compared to PCR or (fish versus catch) or whatever (light have) by fluorescents or by color-emitting,

can all of this be considered as technologically similar or the mechanism of action or platform need to be similar and if they are not similar, can be (man) clinical data enough to mitigate or to show the equivalent?

Ifeanyi Uwemedimo: Thank you for your question so your question is very device-specific and we would recommend contacting DICE to find a representative from OIR to help address your question adequately.

Abdel Halim: Thank you.

Coordinator: And once again to ask a question at this time, please press star then 1. One moment, please.

Irene Aihie: Operator are there any questions?

Coordinator: Thank you, we are showing no further questions. We'll turn it back over to Irene Aihie for closing remarks.

Irene Aihie: Thank you. This is Irene Aihie. We appreciate your participation and thoughtful questions. The presentation and transcript will be made available on the CDRH line Webpage at www.fda.gov/training/cdrhlearn by Friday, November 9th. If you have additional questions about today's presentation, please use the contact information provided in the slide presentation.

As always we appreciate your feedback. Following the conclusion of today's Webinar, please complete a short 13-question survey about your FDA CDRH Webinar series. This 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. That does conclude our conference. We appreciate you attending. You may disconnect at this time.

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