

**Webinar: Final Guidance on Factors to Consider Regarding Benefit-Risk in Medical  
Device Product Availability, Compliance, and Enforcement Decisions**  
**Moderator: Irene Aihie**  
**February 9, 2017**  
**1:00 pm ET**

Coordinator: Good afternoon. And thank you for standing by. For the duration of today's conference, all participant's lines are on a listen only mode until the question and answer session. At that time, if you have a question, press star 1. Today's call is being recorded. If you have any objections, you may disconnect at this time. It is my pleasure to introduce Ms. Irene Aihie. Thank you, ma'am, you may begin.

Irene Aihie: Hello. And welcome to today's FDA webinar. I am Irene Aihie at CDRH's Office of Communications and Education. On December 27, 2016, the FDA issued the final guidance on factors to consider regarding benefit risk and medical device product availability, compliance and enforcement decisions. This guidance document is intended to clarify the FDA's approach to weighing benefits and risks for medical device product availability, compliance and enforcement decisions.

The purpose of today's webinar is to share information and answer questions about the final guidance document. Today's presenter is Ann Ferriter, Director of the Division of Analysis and Program Operations in the Office of Compliance here in the Center for Devices and Radiological Health. Following the presentation, we will open the lines for your questions related to topics in the final guidance only. Additionally, there are other Center subject matter experts available to assist with the Q&A portion of our webinar. Now, I give you Ann.

Ann Ferriter: Thank you, Irene, and good afternoon, everyone. Thank you for joining this webinar discussing the final guidance factors to consider regarding benefit risk and medical device product availability, compliance and enforcement decisions. As Irene said, I am the Director of Analysis and Program Operations within CDRH's Office of Compliance. And I'm very pleased to have the opportunity to speak with you today.

Over the next half hour, I'll be discussing what I believe to be a very significant guidance document to focus the actions of both FDA and industry on decision making in a manner that is in the best interest of the patient and overall public health.

The objectives of today's webinar are to clarify the scope and describe the key elements of the new draft guidance, to outline FDA's motivation behind drafting the guidance, to share the factors the Agency considers when evaluating both risk and benefits in making decisions and to discuss additional factors that should be considered when making these decisions in the best interests of patients, and finally to provide examples of how the agency and industry may apply the guidance.

Before we start on the guidance itself, I'd like to share the why behind why we drafted the guidance. The first and most important reason is to focus on the patients. We, and this is OC (Office of Compliance), OIR (Office of In Vitro Diagnostics and Radiological Health), and ORA (Office of Regulatory Affairs), really strive to make decisions that put the patient first. We take the FDA mission to promote and protect public health very seriously.

Across OC, OIR and ORA, we've always assessed benefit and risk. We wrote this guidance together drawing on the best thinking across the medical device

compliance program so that we can consistently and systematically apply the same factors.

And continuing with why we drafted the guidance, we recognized the FDA was not always aligned with industry and we lacked transparency in our decision making. Through collaboration over the past three years, the industry comments on the guidance, and FDA industry pilots in 2016, we learned more about how to have these constructive benefit risk discussions. The guidance helps to facilitate our conversations and leads towards a focus on quality, patient benefit and consideration of patient preferences.

The guidance states FDA intends to use pilots and other evaluation techniques to help determine how to apply the benefit risk framework. There's a lot of new thinking that we can do. We're already shifting and beginning to apply the benefit risk factors across our work products.

And finally, ODE (Office of Device Evaluation) has drafted three benefit risk guidance documents, the new emerging signals guidance leverages, this thinking across CDRH we have listed our gaze to the patient. This document brings together the compliance staff activities into alignment as well.

This page depicts the front cover of the guidance document which issued in final on December 17, 2016. The draft guidance issued June 16, 2016, and there was a 90-day comment period. In September, we received comments and based on the comments, worked to revise the draft.

The key points, if you don't take anything else away from this discussion, the key points, as you read this guidance, first the guidance is designed to complement thinking and rationale that exists in the pre-market benefit risk

documents. We used the PMA (Premarket Approval) benefit risk documents as a guide during the original drafting.

Second, the guidance is intended to apply broadly to regulatory and compliance thinking and to inform decisions that may impact product availability, potential compliance strategies as well as considering various enforcement options and actions available to the agency.

The goal is to secure the level of compliance necessary to ensure that products on the U.S. market are both safe and effective. And the third purpose of in forming these compliance and enforcement decisions is really to maximize patient benefit.

The webinar today will follow the guidance table of contents. There are six sections in the guidance as well as four appendices. I will review each section in detail. A link to the posted final guidance is provided at the bottom of this page.

In the introduction, the guidance document emphasizes improving clarity for FDA staff and industry as well as maximizing medical device quality and patient safety. We believe that by explaining and gaining a better shared understanding around benefit risk decision-making and compliance, both the agency and industry will be able to better prioritize the use of resources to focus actions that maximize patient benefit, reduce patient risk and improve overall medical device quality.

This benefit risk guidance document encourages not only FDA but also industry to apply the same lens and strategy to addressing potential compliance issues and to take actions that make the most sense for patients.

We provide a little bit of information about the logistics of how FDA will implement the guidance. We've already started by running six pilots in 2016 and then ranging across OC, OIR and ORA and even ODE in many case study discussions. We feel it's especially important to learn from our pre-market folks and therefore have attended their pre-market benefit risk rounds and pulled their pre-market benefit risk assessments. As the Center continues with our strategic priorities, we are learning more about how to gather and use patient information as well as alternative sources of data or real world evidence.

The scope of the guidance is both broad in the range of decisions and narrow in the range of products. Here are a few examples to illustrate the range of decisions where benefit risk factor considerations may be appropriate. Situations where the withdrawal of a violative medical device or recall of a product due to a manufacturer's non-compliance that could result in significant device shortages for patients and their physicians is one of the key places where this guidance would be applicable.

Not every regulatory non-compliance is the same or has the same potential impact to product or patient. As a result, it is important to select the most appropriate regulatory engagement mechanism or action for the situation at hand. What actions, if any, FDA may take when continued access to a non-conforming or device manufactured by a firm with a regulatory compliance issue, those actions must be considered during a shortage situation.

When a recall is indicated, there are a variety of ways in which this recall may be handled. Benefit risk factors may be important devising a recall strategy that is in the best interest of patients.

When should a firm's recall strategy include a correction instead of a removal? Benefit risk factors may also be considered when they are negative inspectional observations during an inspection such as the PMA approval inspection. And then a company may petition for a variance from certain QS (Quality Systems) regulations.

When is it in the best interest of public health to grant this variance? While the range of decisions you could apply this guidance is broad, the area of application is narrow. This document applies to medical devices both diagnostic and therapeutic, but not to devices regulated by CBER (Center for Biologics Evaluation and Research) or combination products where CDRH is not the lead. The guidance document does not apply to EPRC products or other products regulated by FDA such as drugs and biologics.

Section three is really focused on the patient. FDA has the authority to limit the availability of violative medical devices and pursue compliance and enforcement actions related to those violative medical devices. But FDA recognizes that to achieve the Agency's goal of protecting and promoting public health, decisions regarding these actions should be made while focusing on the impact of patients. Failure to consider the short term and long term impact of non-compliance on the benefit risk profile of the device and the benefit risk trade-off of FDA's decision options could result in regulatory actions with unintended adverse effects. For example, the shortage of medical necessary devices.

Section four includes a description of factors to consider. The first part is the factors to consider for the assessment of medical device benefits. The type of benefit includes, but isn't limited to, the medical device's impact on patient health and clinical management. So it's the effect of the device on patient

treatment plans and quality of life, impact on survival and how much the medical device can aid in improving patient function.

Magnitude of benefits is the degree to which patients experience the treatment benefit or the effectiveness of the medical device. The change in patient's conditions or the change in the necessary clinical management may allow FDA to determine the magnitude of the benefit. Then the likelihood of patients experiencing one or more benefits is also key.

The FDA may consider whether there's a subpopulation included in the indication for use that are more likely to retain expected benefits than the overall population. If subpopulations can be identified, the likelihood of those patients experiencing benefit from the device may increase.

The duration effect is how long the benefit can be expected to last for the patient. Knowledge of the duration of treatment may change as the medical device is used.

Another factor is the patient preference on benefit. This is the value that patients place on the use of the medical device. Faced with a severe or chronic disease, a patient may highly value that benefit provided by the medical device in light of the specific condition that the patient has.

For example, patients dying of congestive heart failure may highly value a medical device that extends their lives for a few months. Patients with less severe chronic diseases may or may not place the same value on a device with a short-term benefit.

Benefit factors for health care professionals or care givers include the benefit that they experience by improving the way they care for patients, whether this directly improves patient outcomes or includes clinical practice.

The FDA recognizes that certain devices, such as surgical tools that allow different techniques or devices that positively affect ongoing patient management may improve the benefit profile.

And the last factor we consider is medical necessity. If a medical device provides benefit or addresses unmet needs, this should be a major factor on whether a device would be available for use with patients.

The second section under the description of factors to consider are the factors for the assessment of medical device risks. The severity of harm has always been the first thing we consider. This, like with MDRs (Medical Device Reports), is categorized into three levels. Related deaths or serious injuries, non-serious adverse events which include temporary or medically reversible events, and events without reported harm.

Then we consider the likelihood of risk. And we encourage manufacturers wishing to provide data and calculations to talk with the FDA regarding that information.

We look at whether a non-conforming product has been distributed or not and the duration of the exposure of the population to that non-conforming product. For diagnostics, false positive and false negative results are especially important. As with benefits, we look at the patient's perspective. So the patient's tolerance for risk is the concern the patients have regarding the harm or potential harm caused by the device. Patient tolerance of risk may take into account both the patient's willingness and unwillingness to use a



non-conforming medical device, to use a device manufactured by a non-compliance manufacturer or to tolerate harm, both probable and actual. Risk factors for health care professionals or caregivers may also be considered.

And then the third section under factors to consider is the additional benefit risk factors. These were factors that didn't neatly fall into either benefit or risk, but are critical to FDA's decision-making process. Uncertainty, there's never 100 percent certainty regarding the safety, effectiveness or quality of a device. However, the degree of certainty of the benefits and risks is a factor FDA considers when making decisions.

Mitigations. The actions taken by the manufacturer, by the FDA or other stakeholders to recover benefit limit risk from non-conforming product to address underlying quality system problems or to limit harm. There's different ways of mitigating risk. It could be clinical practice. It could be addressing use errors, looking at the use environment. FDA considers all of these factors and whether the mitigation is proposed or in place in our decision making.

Relating to mitigation, we're concerned with whether the problem for non-conformity can be identified by the manufacturer or by the user.

The failure mode is considered whether it's a systematic failure, or there's a non-conformance that's related to manufacturing, design, use conditions or environment.

We look at the scope of the device issue, whether this is a problem limited to a single lot or batch of devices or whether this problem is inherent to similar devices of this type.

We look at the impact on the patient both if the product is available and if it is not. We talk to patients and understand the preference for availability. And then in a more industry-focused way, we look at the nature of the violations and the type of non-conformance of the product.

And, finally, we consider the firm's compliance history. A manufacturer with a good regulatory history and who has demonstrated initiative in identifying any corrective issues may get a more collaborative opportunity from the FDA.

Since this is an overarching guidance that addresses many processes in compliance and enforcement, the section on how FDA considers benefit and risk is written at a very high level. When FDA looks at benefit risk, it's a fairly straightforward process.

The first thing we do is identify the issue and decide whether the issue requires a benefit risk analysis. We then gather whatever benefit information is available to us. We encourage manufacturers that wish to provide benefit risk documentation to do so through the designated FDA point of contact.

For example, for a recall, you would reach out to the District Recall Coordinator. If you'd like to understand the types of benefit information that would be helpful to share with the District Recall Coordinator, please consider the worksheet in Appendix D.

So after we gather the benefit information, we gather whatever risk information is available to us, the process of systematically gathering risk information is more familiar to FDA and industry. For years, we've been using the health hazard evaluation form. And then FDA considers this list of other relevant factors that I had just mentioned to you.

Section 5 of the guidance describes when benefit risk considerations may be useful in making a product availability decision. These include situations where the firm's recall strategy might appropriately include a correction instead of a removal, includes when deciding what actions, if any, FDA may take when continued access to a non-conforming device or device manufactured by a firm with regulatory compliance issues might be needed or if a market withdrawal would result in product shortage for patients.

Section 5 also notes when benefit risk considerations may be useful in making a compliance and enforcement decision. For example, when it is in the best interest of public health to grant a variance from certain quality system regulatory requirements such as maybe process validation issues if these have been identified during a PMA pre-approval inspection.

Once the benefit risk assessment has been completed, FDA uses this information in several ways. We use this in determining the adequacy of a manufacturer's proposed correction strategy or mitigation and would use this information in determining whether an observed violation requires a warning or an entitled letter or an alternative less formal approach.

For product availability decisions, we'd use benefit risk factors to consider whether a patient should have continued access to the device or whether we should take steps to limit product availability.

For compliance and enforcement decisions, we'll use benefit risk to consider when we might work with a manufacturer to address the underlying issues or when it was time to take a more formal compliance for enforcement action.

Section 6 of the guidance provides specific examples of how benefit risk assessments may be applied, including benefit risk factors discussed today as

well as the more general factors like uncertainty and potential mitigations. Each example addresses a key situation, such as a circumstance in which a recall may generate a shortage and then walks the reader through logic and decision making required to do the benefit risk assessment.

The specific examples include recall and shortage generation, a variance petition and continued access to a non-conforming product. After reading the comments on the draft guidance, we added IVD (In Vitro Diagnostic) and a rad(radiological) health example. The examples related to compliance enforcement decisions include an evaluation of whether to send a warning letter or take an alternative approach and an evaluation of potential actions following an inspection of a manufacturer with observed quality system deficiencies.

Appendix A of the guidance describes the intersection with ISO (International Organization for Standardization) 14971. ISO 14971 is an FDA recognized standard and assuring conformity with this standard may help device manufacturers meet requirements specified in FDA regulations. The documentation of risk management decisions by manufacturers may help streamline these decisions for both FDA and manufacturers producing outcomes for patients that deliver the most benefit for the least amount of risk and providing a reasonable assurance of safety and effectiveness.

And finally, in Appendices B, C and D the guidance provides a series of worksheets for both FDA and the manufacturers to facilitate good benefit risk decision making.

Appendix B contains a worksheet to help us think through benefit in a systematic way. Using the seven factors that I described that were type of benefit, magnitude of benefit, likelihood of patients experiencing one or more

of benefits, duration of effect, patient perspective on benefit, benefit factors for health care professionals and medical necessity. The worksheet provides a series of questions that strengthen our understanding of benefits. For example, the questions on this slide relate to the magnitude of benefit and the patient perspective on benefit.

One of the key elements of benefit is medical necessity. And we have questions in Appendix B that help us consistently and systematically think through what is meant by medical necessity.

Appendix C is used for risk assessment, including serious events as well as an assessment of temporary or non-serious events. As with Appendix B, Appendix C is organized around the seven factors related to risk, like severity of harm and likelihood of risk as shown on this slide.

And the last Appendix B slide has questions related to non-conforming devices and patient tolerance of risks. Appendix D contains those other factors. Nine factors that don't fit neatly as benefit or risk but are needed in making product availability, compliance and enforcement decisions. These factors included uncertainty, mitigation, detectability, failure mode, scope of the device issue, patient impact, et cetera.

The questions on this slide focus on uncertainty and impact to the patient.

And on the final slide this shows some of those other factors and questions related to the nature of violations for non-conforming product as well as firm compliance history.

So this concludes the presentation part of today's webinar. I hope the description of the guidance document has been helpful. I'm going to turn the mic over now and we'll open it up for questions.

Coordinator: Thank you. If you would like to ask a question, please unmute your phone, press star followed by the number one. And when prompted, record your name clearly so I may introduce you. To withdraw your question, press star two. Again, to ask a question, star one.

We have one question from (Elise Mensias). Go ahead. Your line is open.

Irene Aihie: Operator, do we have any other questions?

Coordinator: I show no additional questions at this time. As a reminder, if you would like to ask a question, press star followed by the number one. One moment please.

Our next question comes from Mark McCarty. Go ahead, your line is open.

Mark McCarty: Hi. Thank you very much for taking the question. Ann, you mentioned something about six pilot projects that you have related to this guidance. I was wondering if you could offer a little bit more detail on those.

Ann Ferriter: Sure. Because this is a broad overarching guidance, we ran a series of pilots in 2016 to understand how this guidance document related to processes within the Office of Compliance, OIR and ORA. So we ran a pilot looking at allegations of failure to submit appropriate pre-market submissions. We looked at allegations of issues in clinical trials. We looked at EIR reviews, recalls. And we did a series of case studies.

Mark McCarty: Can you talk a little bit about some of things you learned from the pilots?

Ann Ferriter: Sure. So we learned that we're a lot more skilled in understanding risk than we are in understanding benefit. And that we have ready access to risk information but working with a company to understand benefit and understand the landscapes that this device was operating in was a little bit more challenging for both FDA and industry. And so we really had to take a step back and develop some basic questions, basic forms so that we would consistently gather similar information on benefit.

Mark McCarty: All right. Super. Thank you very much.

Ann Ferriter: Thank you.

Coordinator: Our next question comes from (Linda Chapman). Go ahead, your line is open.

(Linda Chapman): Thank you for the walkthrough on the guidance document. It was very helpful. My question is around whether it would be beneficial for private industry to follow some of the rationale in the guidance document as they do their internal risk benefit analysis.

Ann Ferriter: We believe it would be very helpful. This guidance document was written to better align FDA and industry. And so as industry adopts looking at these same factors in considering benefit risk in the same way, we believe that we'll have more constructive conversations.

(Linda Chapman): Thank you. So if a company did that and those risk management analyses were in their files when FDA inspected, would that have positive effect maybe on the inspection itself?

Ann Ferriter: Since you included the word maybe, absolutely. So, of course, this would be a case-by-case basis. Every investigator would be looking for particular things. And there could be a case where a firm has documented benefit risk assessment as per the guidance and not gotten it right. So we're going to leave that possibility open.

But by using the guidance, what you do is you start on the same page as that investigator.

(Linda Chapman): Okay, great. Thank you very much.

Ann Ferriter: Thank you, Linda.

Coordinator: Our next question comes from Karen Hughes. Go ahead, your line is open.

Karen Hughes: Hi and thank you. Couple questions. So one for certain submissions, for example, for a de novo, a risk benefit determination using the worksheets in the other risk benefit guidance which look like they overlap quite well with what's in this guidance, are generated by FDA and the applicant.

And so I was wondering, there is, of course, a summary of that, for example, in a de novo summary on the FDA Web site. How might that be used by FDA when it exists? And, I think, you also mentioned you, in the case of a recall, you might reach out to the district coordinator. How is that communication that that information exists or is that only viewed as value at the time of the application for the de novo?

Ann Ferriter: Absolutely. We very much value the benefit risk assessments that have been conducted by the pre-market staff. And we have direct access to them. So on the FDA side, we'll be using them. I would recommend companies also, if



they're interested in sharing the pre-market analysis with the recall coordinator, that would be a good step. The recall coordinator will also have access to that. But perhaps they missed it. So it's never a bad idea to share it again or emphasize the importance of the analysis.

Karen Hughes: Great. Thank you. And then just one other question, I know the guidance is now released and no longer in draft. But I didn't know if there would be an opportunity at any other time, maybe even on device advice.

I'm a diagnostics manufacturer. And while I found - I'm grateful that you included a test as an example in the guidance, the pregnancy test, it's kind of an easy example because the patient is directly involved. But it doesn't really cover all of those hospital tests where it's a little harder sometimes for maybe the patient to be able to say what their direct benefit is because it's "to them just another lab test."

So just some feedback that if there is an opportunity for something, you know, anything like a Troponin versus maybe something that would be considered lowered risk, which I can't think of off the top of my head, but something like that might be of value as well.

Ann Ferriter: Thank you for that feedback, Karen.

Coordinator: Our next question comes from (Padmini Sahoo). Go ahead, your line is open.

(Padmini Sahoo): Hi. This is Padmini, I had a question regarding compliance and enforcement. So when there is non-conformance that has been identified for distributed products, we usually have the ETT, or the health risk assessment form that FDA requires. I was just wondering if there would be an additional risk benefit assessment form that would be required or with this guidance

document being published is there an additional requirement for companies to provide their current risk files when reaching out to FDA during enforcement decision making?

Ann Ferriter: So this guidance document does not add an additional requirement to provide additional information. You mentioned the HHE (Health Hazard Evaluation) form. Our vision is that over time we'll modify the HHE form to incorporate benefit so that you could see how FDA considers it in our health hazard evaluations.

(Padmini Sahou): Will that be in line with this guidance document in the future like...

Ann Ferriter: Yes.

(Padmini Sahou): And being from a regional diagnostic industry, I'm not sure, like, what patient perspective. I don't think we have that much of information. It's really the information from, I would say, the physician setting, or the clinical setting about, you know, them making an assessment about the benefits rather than the actual patient perspective. Would you have any advice on that because we have, like, you know, medical affairs personnel or, like, someone at that position making this assessment of how beneficial or how much risk would a non-conforming device boast to a patient, but not really having a perspective from the patient itself.

Ann Ferriter: Right. And this would be a device-by-device analysis that you would do. But there will be some devices that there isn't a strong signal from a patient perspective. We understand that.

(Padmini Sahou): Okay.

Coordinator: Our next question comes from (Debbie Connors). Go ahead, your line is open.

(Debbie Connors): Thank you very much. Ann, thank you for the presentation. And just looking at what you've gone through on the slide deck, it appears that the guidance talks a lot about the what's of the information that FDA considers in this decision-making process.

What I'd like to understand a little bit more is how does FDA once you've gathered all of this data, how do you rank it and how do you aggregate it as part of your analysis and decision-making process for whether a violative product should stay in the field or what action should be taken against a manufacturer?

Ann Ferriter: So I think that's next step. We've got a lot of questions, a lot of comments on the guidance about how were different factors weighted and what was the ranking of different factors. And we don't have all those answers yet.

What we've done now is standardized the factors for consistency and create the detailed worksheets so you can see our thought process. But the actual ranking and any kind of algorithm that would help us establish whether something should have non-regulatory or regulatory approach has not been developed yet. And we're working with ORA and OIR to get all of that.

(Debbie Connors): Can I ask a follow-up?

Ann Ferriter: Yes.

(Debbie Connors): Is that an activity that you will be piloting as well? And are you going to within industry look at examples within industry when you pilot that?

Ann Ferriter: I would say yes. I can't commit all of our FDA resources, but I think piloting within an industry would have significant benefits.

(Debbie Connors): Thank you.

Coordinator: I show no additional questions at this time. But as a reminder, if you would like to ask a question, please unmute your phone, press star 1 and record your name clearly when prompted so I may enter it with your question. Again, star 1 to ask a question. One moment please for incoming questions.

I show no additional questions at this time. I'd like to turn the call back to Irene Aihie.

Irene Aihie: Thank you. This is Irene Aihie. We appreciate your participation and thoughtful questions. Today's presentation and transcript will be made available on the CDRH Web page at [www.fda.gov/training/cdrhlearn](http://www.fda.gov/training/cdrhlearn). That's Friday, February 17.

If you have additional questions about the final guidance document, please use the contact information provided at the end of the slide presentation. As always, we appreciate your feedback. Please complete a short survey related to today's webinar. The survey can be found at [fda.gov/cdrhrwebinar](http://fda.gov/cdrhrwebinar). Again, thank you for participating. This concludes today's webinar.

Coordinator: This concludes today's conference. Thank you for participating. You may disconnect at this time.

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