NWX-FDA OC

Moderator: Irene Aihie
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Coordinator: Welcome and thank you for standing by. At this time all participants are in a listen-only mode until the question and answer session of today's call. At that time if you'd like to ask a question please press Star 1. Today's conference - throughout the conference questions will only be accepted over the phone today.

Today's conference is being recorded. If you have any objections you may disconnect at this time. I would now like to turn the meeting over to Irene Aihie. Thank you and 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 On June 15, 2016 the US Food and Drug Administration published a draft guidance document Factors to Consider Regarding Benefit Risk in Medical Device Product Availability, Compliance and Enforcement Decision. The draft guidance focuses on the factors the FDA may consider when making decisions related to compliance and enforcement action for a specific medical device company or when making decisions that may affect medical device availability on the market in general.

The focus of today's Webinar is to share information and answer questions about this draft guidance. Your presenter will be Robin Newman, Director of the Office of Compliance here in the center. Following the presentation we will open the lines for your questions related to the topics in this guidance

draft only. Additionally there are other centers subject matter experts available to assist with the Q&A portion of our Webinar. Now I give you Robin.

Robin Newman: Thank you Irene and good afternoon everyone. As you heard from Irene my name is Robin Newman. I joined CDRH in February of this year as the new Director of the Office of Compliance. And I'm very pleased to have the opportunity to speak with you today. Over the next few minutes I will be discussing what I believe may be a very impactful proposed guidance document and in our journey to focus the actions of both FDA and industry for decision making that is in the best interest of the patient and overall public health.

The objectives for today's Webinar are to clarify the scope and describe key elements of this new draft guidance, to describe FDA's motivation behind the development of this guidance and encourage your comments to the docket, to define factors the agency is proposing be considered when evaluating both risk and benefits in making product availability decisions as in the case with potential for recall and taking compliance or other types of enforcement action, to discuss additional factors that should be considered in making decisions in the best interest of patients and to provide examples of how the agency and industry may apply this guidance.

This page depicts the front cover of the draft guidance document. Note that the draft was first issued on June 15, as opposed to June 16, that's the day it posted. And it's currently open for comments through mid-September. As a result I will be providing you with our current thinking for educational purposes, but actual guidance language may change as we receive and review your comments. Later during our Q&A I will be joined by, as you heard from Irene, several subject matter experts including Ann Ferriter a key author of this guidance and together we will try to answer any questions that you have.

As you peruse the draft guidance there are several key points that we ask you to bear in mind. First this guidance is designed to complement thinking and rationale that exists in similar premarket benefit risk guidance documents. Second it is also designed to better align the actions and thinking of FDA to those taken by industry. Number three the guidance is intended to apply broadly to regulatory and compliance thinking to include decisions that may impact product availability, potential compliance strategies, as well as considering various enforcement options and actions available to the agency designed to secure the level of compliance necessary to ensure that products on the US market are both safe and effective.

FDA is aware that there is a potential for compliance or enforcement decisions to have a negative impact on patients or patient care. As a result this guidance seeks to provide a framework within which patient needs, desires and potential benefit are considered when making those decisions. In the guidance we have attempted to describe various factors that may be taken into account when considering patient benefit risk. And we provide examples and worksheets to assist manufacturers as well as the agency in choosing the best pathway forward when a noncompliance occurs.

On the following slides I will discuss the factors that we've identified as key to making the most effective benefit risk compliance decision. As noted earlier, however, we are eager to receive your comments for consideration before finalizing this guidance and it is very possible that the list of factors may change as a result. Using a benefit risk lens is not a new or novel approach for the agency. In fact, the Office of Compliance always strives to make decisions in concert with what is best for patients and public health. With this guidance, however, we are trying to clarify and add transparency to the types of factors that are considered and to share this thinking with

industry. The key goal is to better align decision making and action for both FDA and the manufacturer.

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, to take actions that make the most sense for patients. For example, when a manufacturer produces a product known to be nonconforming or has other issues that threaten compliance, the most appropriate response may or may not be a field action, recall, or market withdrawal when a patient benefit or needs are considered.

Here are a few examples to illustrate the scope of the types of decisions where benefit risk factors considerations may be appropriate. Situations where withdrawal of a violative or medical device or recall of a product due to manufacturer noncompliance may result in significant device shortages for patients and their physicians. Two, not every regulatory noncompliance is the same, or has the same potential impact to product or patient. As a result, it's important to select the most appropriate regulatory engagement mechanism or action to the situation at hand.

Three, when a recall is potentially indicated there are a variety of ways in which this may be handled. Benefit risk factors may be important in devising a recall strategy that is in the best interest of patients. And four, benefit risk factors may also be considered when there are negative inspectional observations during the PMA approval inspection and a petition for variance from certain QS regulation is requested.

Other factors, described in this document that can apply a benefit risk structure to, are product availability and issues around compliance and enforcement decision making. FDA has authority to limit the availability of violative medical devices and to pursue other compliance and enforcement actions related to these violative medical devices. 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 impact on patients. Failure to consider the short term and long term impact of noncompliance on the benefit risk profile of the device and the benefit risk trade off of FDA's decision options on health and quality of life for patients could result in regulatory actions with unintended adverse effects for example a shortage of medically necessary devices.

In certain situations involving risk of patient harm, FDA and industry individually or collaboratively can help maximize benefit and reduce risk to patients by assessing the situation, considering the patient's perspective, evaluating any regulatory noncompliance or device nonconformity in light of a benefit risk profile for the device, factoring in alternatives where available, considering the benefit risk trade-off for patients of each decision option and then determining the most appropriate next step.

So let's discuss the factors that should be considered when determining medical device risk. The assessment of risk severity: in the guidance risk is categorized into three levels and includes a duration component. The three levels of risk are medical device related deaths or serious injury, risk characterized as non-serious adverse events, risk associated with events without reported harm to patients or user.

The assessment of nonconforming product risk: this includes assessing whether a nonconforming product has been placed in distribution and if so how many nonconforming devices are on the market.

The assessment of duration of exposure to the population: this dimension asks that we assess the length of time between initial patient exposure to the device with risk of harm and the point when risk of harm has been successfully addressed. This includes the possibility of managing potential for harm through appropriate and successful mitigation. The assessment of potential for false positive or false negative results: if a diagnostic medical device gives a false positive result, the patient may be incorrectly diagnosed with a serious disease and receive an unnecessary treatment. If a device diagnostic medical device gives a false negative result, the patient may not be diagnosed with the correct disease or condition and might not receive an effective treatment. The impact of false positives or false negative results may vary with disease state, diagnosis, or toxicity of treatment, and these may all be considered as part of this assessment.

The assessment of a patient's tolerance for risk: this assessment addresses the level of concern that patients may have regarding 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 the nonconforming medical device, to use a device manufacturer - manufactured by a noncompliant manufacturer, or to tolerate harm both probable and actual harm. And finally reassessment of risk factors for healthcare professionals and caregivers. Risks to the user may be considered when the risk may have an adverse impact on the clinician or caregiver or on their ability to use the device safely and as directed.

Risk alone however is not the only consideration in making a balanced assessment. There are also medical device benefit factors to be considered to achieve product availability, compliance or enforcement decisions that reflect a true benefit risk outcome. For example, factors that should be considered when determining medical device benefit might include the type of benefit. This includes but is not limited to the medical devices impact on patient health and clinical management i.e. 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 benefit: this is the degree to which patients experience the treatment benefits or the effectiveness of a medical device. For example, the magnitude of change in a patient's condition or the change in the level or type of necessary clinical management may allow FDA to determine the magnitude of benefit.

The likelihood of patients experiencing one or more benefit: FDA may consider whether there are subpopulations included in the indication for use that are more likely to retain expected benefits than the overall population. If the subgroups can be identified, the likelihood of those patients experiencing benefits from the device may increase. Duration of effect: how long the benefit can be expected to last for the patient. The FDA also recognizes that knowledge of the duration of treatment effect may change as the medical device is used. So information gained with greater device experience may be critical here.

Patient preference regarding benefits: this is the value that patients themselves place on the use of the medical device. A patient faced with severe or chronic disease may highly value the benefit provided by a medical device in light of the specific condition that patient has. For example patients dying of

congestive heart failure may highly value a medical device that extends their life for a few months. Patients with less severe or chronic diseases may or may not place the same value on a device with shorter term benefits.

Benefit factors for healthcare professionals and caregivers: this may include the benefit that healthcare professionals or caregivers experience by improving the way that they care for patients, whether this directly improves the patient outcome or improves clinical practice. FDA recognizes that certain devices such as surgical tools that allow different techniques or devices that positively affect ongoing patient management such as shortening the duration of procedures or decreasing the number of additional treatments required may improve the benefit profile.

Medical necessity: if a medical device provides benefits or addresses needs unmet by other medical devices or therapies, an assessment of whether another medical device or therapy could be used in substitution and the availability of that other medical device or therapy may be extremely important.

Finally there are several other more general factors that may be important in determining the best regulatory or compliance decision from a patient's perspective. First, there is the level of uncertainty. There is never 100% certainty regarding the safety, effectiveness or quality of a medical device, however, the degree of certainty of benefits and risk of the device is a factor that FDA considers when making benefit risk assessment.

Second, what mitigations are available and what is the likelihood that they can manage risk? Mitigations are actions taken by the manufacturer, by FDA, or by other stakeholders to recover benefit to limit risk from nonconforming products and to address the underlying quality system problem or to limit

harm. Mitigations could address clinical practice, use errors, unmet medical needs, the use environment, user population, user skill level, clinical understanding and assessing risk, current expectations and clinical use, any changes in medical practice and the use of the product in an emergency or crisis situation.

A third additional benefit risk factor to consider is detectability. This is whether or how easily a nonconformity can be identified either by the manufacturer or by the user. Failure mode is also a consideration. Failure mode addresses the specific method or type of failure. And this may be used to identify the cause of the nonconformity for instance whether the nonconformance is related to manufacturing, to design, conditions of use or to the environment. The scope of the device issue should also be evaluated. To assess whether risks identified are inherent to similar devices of this type. In other words, if the nonconformity reports potential harm that we are observing associated with a specific manufacturer only or does it extend to an entire category or class of products?

Patient impact, impact on the health, and quality of life of patient: FDA, and where appropriate, industry, should consider whether patients are better off if the device is or is not available. And related to patient impact, caregiver preference for availability is also a factor. FDA, and industry where appropriate, should consider whether patients and caregivers would prefer to have access to the device and whether they adequately understand the related benefits and risks.

The final broad factors to consider are the nature of violations or nonconforming product. This may include whether the violation was systemic or non-systemic in nature as well as the extent of any non -product conformity. And finally the firm's compliance history. The manufacturer's

regulatory history and initiative in identifying and correcting problems is a key factor in making the most appropriate benefit risk compliance decision. Examples of this may be firms with chronic or repetitive issues that have not been addressed, manufacturers who are in communication with FDA have been either lacking or inadequate, or firms that consistently fail to maintain manufacturing standards and meet regulatory requirements.

When FDA looks at benefit risk it's a fairly straightforward process. The first thing we want to do is identify the issue, gather whatever benefit information is available to us, gather whatever risk information is available to us, and then consider this list of relevant other factors that I just mentioned for you. Section 5 of the guidance provides examples of situation where benefit risk considerations may be useful in making product availability decision. These include situations when a firm's recall strategy might appropriately include a correction instead of a removal, includes when acting - when deciding what actions if any FDA may take when continued access to a nonconforming device or a device manufactured by a firm with regulatory compliance issues might be needed if market withdrawal would result in product shortage for patients.

When considering the answer the question, what is in the best interest of the public health, to grant a variance from certain - when it is in the best interest of public health to grant a variance from certain quality system regulatory requirements for QS issues identified through a PMA pre-approval inspection for example when issues of process validation issues are identified during inspection. When deciding when FDA might choose to exercise enforcement discretion and not take immediate action against a company for marketing a device or a significant change or modification has been made prior to obtaining regulatory clearance as is required in 21 CFR 807.81(a)(3).

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

It is also important to consider the context in which the regulatory or compliance decision must be made. For example a situation where we have high patient benefit coupled with low or little risk is more likely to result in a decision to work with the manufacturer to address the underlying issue without enforcement action. On the contrary, in a situation where we have low benefit risk or low patient benefit with higher risk, this would more likely result in an enforcement action to address the problem.

Section 6 of the guidance provide specific examples of how benefit risk assessments may be applied, including the benefit and risk factors discussed today as well as the more general factors such as uncertainty and potential mitigation. Each example provided addresses key issues such as a circumstance in which a recall may generate a shortage, and walks the reader through the logic and decision making required to do the benefit risk assessment. Specific examples included are recall shortage, evaluation of variance petition, and continued access to nonconforming products. And examples related to compliance and enforcement decisions including - include evaluation of whether to send a warning letter or take an alternative approach and evaluation of potential actions following an inspection of the manufacturer with observed quality system deficiency.

In addition, Appendix A of the guidance describes its intersection with ISO 14971. ISO 14971 is an FDA recognized standard and assuring conformity

with this standard may help device manufacturers meet the requirements specified in FDA regulations. Both ISO 14971 and 24 - 21 CFR part 820 take a total lifecycle approach to management of risk associated with medical devices. Good documentation of risk management decisions by manufacturers may help to streamline these decisions for both FDA and manufactures producing outcomes for patients that deliver the most benefit with the least amount of risk and providing a reasonable assurance of safety and effectiveness.

Finally, in Appendices B, C and D, the guidance provides a series of worksheets for both FDA and the manufacturer may use to facilitate good benefit risk decision making. Note that this worksheet should be used in benefit assessment and assesses impact and clinical management and patient health. It also prompts for assessment of any additional patient benefits, and on the following page discusses things such as magnitude of benefit for the patient.

Appendix C is used for risk assessment, including serious adverse events as well as an assessment of temporary or non-serious adverse events. And Appendix D assists in the decision of the broader factors such as uncertainty and mitigation that are so important in understanding the complete benefit risk balance of a given situation. So, to scope, patient impact, lack of availability, preference of availability, potentially the same topics that we were talking about earlier, and again, patient impact related to inspectional findings and the nature of those violations or findings.

And then finally the firm's compliance history. Again, as we discussed earlier, a firm with a history of significant noncompliance or failure to respond to the agency appropriately is negatively - is considered a negative factor in the benefit risk assessment.

So this concludes this portion of today's Webinar. Please note that the comments are due on September 14 for the guidance and we are very eager to receive and discuss your comments and see how they will be integrated into the guidance as it's finalized. I'm going to turn the mic over now and open for questions.

Irene Aihie: Thank you. We'll now take questions.

Coordinator: If you'd like to ask a question, please press Star 1 and record your first and last name clearly when prompted. Your name is required to introduce your question. Once again if you'd like to ask a question please press Star 1.

Irene Aihie: One second as the operator…

Coordinator: First question is from Dr. (Michael). Your line is now open.

Dr. (Michael): Yes hello. You mentioned that one of the aspects that you were looking at was whether or not the public accurately understands the benefits and risks and how are we supposed to calculate or figure that? Do you – is there a methodology that you're proposing? Thank you.

Robin Newman: There's not a - thank you very much for the question. There's not a specific methodology that we are proposing at this time although certainly if there are comments to that we would be open to hearing it. The - this is never one of those things that's incredibly black and white it is always going to…

Dr. (Michael): No.

Robin Newman: …require a certain amount of judgment on the part of both the agency as well as the manufacturer.

Dr. (Michael): Well yes I appreciate that. You know, it's just that part of the regulatory process is there in place because especially with medical devices that there's a lot of a difference between the knowledge of the manufacturer and that of the public. And that, you know, that causes some kind of sometimes a fallacy that we can have the public be as knowledgeable as they may need to be in order to understand the true risks. Thank you.

Ann Ferriter: Exactly. That's a great question. And FDA has actually drafted a full guidance just to explore getting patient preference information. And I'd invite you to contact DICE with that specific question and they can provide information about gathering patient preference information.

Dr. (Michael): Thank you so much.

Robin Newman: And you can see the DICE email on the screen now.

Robin Newman: We'd like to take our next question.

Coordinator: Next question is from (William Hyman). Your line is now open.

(William Hyman): Thank you. I - this is a two-parter. How do you propose to combine different aspects of either risk or benefit to get an overall picture? And how do you - are you proposing to actually compare benefits to risk? Thank you.

Irene Aihie: One second as we gather that question and get that answer for you.

Robin Newman: Mr. (Hyman) I appreciate the question. It's a very good one. One of the things that we're encouraging and you'll see this in the guidance document is to really utilize the clinical expertise of the physicians and clinicians that we have here within FDA as well as frankly the clinicians and physicians that we work within industries and that companies have within their domain. This is a critical piece of this assessment and it is necessary in order to ensure even to the previous callers question that we have adequate information to do that type of assessment.

Irene Aihie: Are there any other questions?

Coordinator: I'm showing no further questions at this time.

Irene Aihie: We'll wait one second for some more questions to pop into the queue.

Coordinator: Once again I'd like to remind all participants if you'd like to ask a question please press Star 1.

Irene Aihie: It looks like we have a few more questions in queue.

Coordinator: Yes. Our next question is from (Brian Maitland). Your line is now open.

(Brian Maitland): Yes. It seems that the first question that was asked can only be responded to reasonably by saying that the disclosure on the part of the medical device maker has to be adequate so that not only the physician or healthcare professional but also the patient can reasonably understand and properly assess whether or not the risks and benefits are appropriate for that patient. Thank you.

Robin Newman: Thank you. I would agree with that absolutely.

Irene Aihie: Our next question please.

Coordinator: Just a moment. This question is from Dr. (Heather). Your line is now open.

Dr. (Heather): Yes. My question is related to at what part of the process would the risk benefit analysis be appropriate on the manufacturer's side? Should we be incorporating that into the health hazard evaluation or at what juncture?

Robin Newman: So I would absolutely recommend that you incorporate it at the time of the health hazard evaluation. As part of - again look at the interface to 14971, look at the things you're doing to do your risk assessment and mitigation activities and then making this part of sort of that whole product lifecycle. Remembering also to go back and revisit those risk assessments as you have more experience with the product and you have more information coming in with regard to everything from user interface, to patient toxicities to the overall experience that patients have with these products. And this does require honestly a sort of proactive seeking information from the customer that does not always happen. And I would strongly encourage that as well because that's where the most information lives and breathes.

Dr. (Heather): Thank you very much.

Ann Ferriter: And this is Ann Ferriter. I'd like to add also in our conversations with the FDA you might consider doing a benefit risk analysis and sharing your perspectives with FDA. This may be especially helpful in prioritizing a response to any observed violations.

Robin Newman: I would really encourage that as well. I think that's a very good point Ann because a lot of times what happens is the violation is observed the product

may be important, patients may benefit from it. You may have an 80% market share I don't know. But unless we have information that helps us understand exactly what you know in terms of risk of your product and how then we can do what we can do with regard to any sort of mitigation or balancing that, et cetera, it's impossible for the FDA to I think really effectively utilize this analysis.

Dr. (Heather): Thank you again.

Robin Newman: Welcome.

Coordinator: The next question is from (Miraj Katel). Your line is now open.

(Miraj Katel): When is the FDA going to recognize that the Part A and Part B of medical insurance is required for protecting and promoting public health?

Robin Newman: I'm sorry I'm not sure I understand your question.

(Miraj Katel): To protect and promote public health there is public health insurance and Social Security's (banded) profile system. These Webinars are for a government recovery audit.

Robin Newman: Okay. I understand what you're asking.

(Miraj Katel): What of my Part A and Part B eligibility dates?

Robin Newman: I understand. I believe that question is frankly a bit out of scope for this particular conversation but I have written it down and I think it's something to consider. Thank you.

(Miraj Katel): Thank you.

Coordinator: I would like to remind all participants if you have a question please press Star 1. Our next question is from (Adin Macuti). Your line is now open.

(Adin Macuti): Hi. I have a question related to MDRs in the field or assessing risk. So there is a comment on one of the slides saying that if the risk is generally acceptable by competitors or in the industries this is something common that should be playing a part in the risk benefit assessment other than MDR that we can see or what feedback we can get from clinicians? I was trying to understand what's the best way to kind of document say we see an issue in the field and we know this is generally acceptable for that particular type of device how would you go about documenting that other than what you see in terms of MDRs on an FDA mod database?

Robin Newman: So generally what I would turn you to is the risk management file within the manufacturing environment. Take a look at the risk assessment. Take a look at how that file has been managed over time. Take a look, make sure that they are - as new information has become available the file has been updated the risk profile has been updated. Additional mitigations may be necessary as more experience is - or is gained. So this is the kind of place that I would look for internally to in the manufacturing environment specifically for that kind of information.

(Adin Macuti): Okay. Okay thank you. And from an external perspective if I could have a follow-up question, what would be - what would you recommend documenting? So when you - if you are linking your health hazard evaluation to a risk benefit assessment and other than your risk management files internally what else would you think would be a good way to look at like this

type of issue is generally acceptable like do you have any thoughts on that, that you can share with us.

Robin Newman: I'm going to give you some thoughts. I will tell you this is my opinion so it may…

(Adin Macuti): Okay.

Robin Newman: …or may not reflect the thinking of the agency. And just based on the fact that many of you may know that I've actually joined FDA coming from industry so I have some experience in terms of what we have done. One of the most important things I believe the company can do is be very vigilant in their environmental scanning. Do not rely entirely upon the complaint files or something - or those types of reports that come in say from sales marketing, service, et cetera, to give you your whole profile. You really have to have a proactive risk management environmental scanning process where you're looking for everything from new publications, to talks that were given at an ACC to whatever it is to help you have a really full and comprehensive understanding of what's happening with your product. This also frankly gives you visibility into new populations, off label use, and a variety of other things that can introduce risk to the product that was not originally conceived at the time it was developed.

(Adin Macuti): Thank you so much.

Robin Newman: You're welcome.

Coordinator: I'm showing no further questions at this time.

Irene Aihie: Thank you. This is Irene Aihie. And we appreciate your participation and thoughtful questions..

If you have additional questions about the draft guidance document please use the contact information provided at the end of the slide presentation. Today's presentation and transcript will be available on the CDRH Learn webpage at www.fda.gov/Training/CDRHLearn, by Tuesday, July 19th. Please submit draft guidance related comments to docket number: FDA-2016-D-1495 by September 14, 2016. The docket can be found at https://federalregister.gov/a/2016-14200. If you have additional questions about the draft guidance document, please use the contact information provided at the end of the slide presentation. As always, we appreciate your feedback. Again as always we appreciate your feedback. Thank you for participating. And this concludes today's Webinar.

Coordinator: This now concludes today's conference. All lines may disconnect at this time. Thank you.

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