Guidance for Industry and FDA Staff:
Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications

Hello. My name is Elias Mallis, the Director of the Division of Small Manufacturers, International and Consumer Assistance at FDA's Center for Devices and Radiological Health (CDRH). Welcome to CDRH Learn.

CDRH Learn is a web-based training program that provides Industry education on matters pertaining to medical devices and radiation programs. This program consists of a series of training modules that address timely matters that FDA believes you will find informative and interesting.

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Today I am going to discuss the guidance document entitled, Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications.

This guidance document was published in its final form on March 27, 2012. It will apply to all premarket approval (or PMA) and de novo classification decisions made beginning May 1, 2012.

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This guidance document was developed to identify and clarify the factors FDA considers when making benefit-risk assessments in PMA applications, and de novo classification petitions for medical devices. FDA believes that the full implementation of the guiding factors described in this guidance will facilitate transparency, consistency, and predictability of the premarket benefit-risk assessment process.

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This guidance addresses two main avenues for a sponsor to gain market entry for a new medical device: PMAs and de novo classification petitions, or de novos.

Under Section 513(a) of the Federal Food, Drug & Cosmetic Act, or the "FD&C Act," FDA determines whether PMA applications provide a "reasonable assurance of safety and effectiveness" by "weighing any probable benefit to health from the use of the device, against any probable risk of injury or illness from such use."

In its review, FDA evaluates any valid scientific evidence submitted in the application and determines whether it supports the intended use of the device. This evidence may come from a range of information sources, including clinical data, animal studies, and non-clinical data.

When eligible, a sponsor may submit a de novo classification petition in order to gain market entry for a new medical device. For de novos, FDA conducts a complete benefit-risk assessment and makes a classification determination under Section 513(a)(1) of the FD&C Act. The classification determination considers all the risks of the device and whether the risks can be mitigated sufficiently through general and/or special controls.

Devices that reach the market via the de novo process can serve as predicates for future 510(k) submissions.

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This guidance document applies to PMA applications and de novo classification petitions. The factors described in the guidance should be considered during the design, development, and assessment stages of these submissions.

This guidance applies to both therapeutic and diagnostic devices.

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This guidance was developed by CDRH's benefit-risk working group, made up of staff from the Office of Device Evaluation (or ODE), the Office of Surveillance and Biometrics (or OSB), the Office of In Vitro Diagnostics (or OIVD), and the Office of Science and Engineering Laboratories (or OSEL).

Regarding the key milestones for this document, the guidance was published in draft in August 2011. A docket was then opened for public comments through November 15, 2011. Next, the comments were collated, addressed, and incorporated as appropriate into this final guidance.

The final guidance document was issued on March 27, 2012.

And finally, FDA reviewers will use this guidance document for all decisions beginning May 1, 2012.

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This guidance document addresses and defines multiple factors that FDA considers important in making benefit-risk determinations. It provides several examples of how the factors are applied.

A worksheet is provided at the end of the guidance. This worksheet is designed to capture how FDA reviewers should consider the factors described within the guidance when making benefit-risk assessments.

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In the next part of this presentation, I will describe the various factors that FDA reviewers will use when making benefit-risk determinations. I will present each factor and give a few examples of the types of questions that FDA reviewers consider for each factor. The guidance document contains a worksheet in the Appendix that provides additional questions for each factor.

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The guidance places the factors used in benefit-risk determinations into three primary categories: the factors that characterize the benefits of the device; the factors associated with the risks of the device; and additional factors that affect the overall benefit-risk determination.

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The "benefit" factors in the benefit-risk determination include the type of benefits, the magnitude of the benefits, the probability of the patient experiencing one or more of the benefits, and the duration of the benefits. These factors are considered individually and in the aggregate.

First is the type of benefit. The type of benefit can be measured directly, or by using endpoints or surrogate endpoints. The endpoints, and the value physicians and patients place on the benefit, are important considerations. In addition, it is important to understand the impact of the benefit on public health, especially for therapeutic devices and early diagnosis of disease.

The second benefit factor is the magnitude of the benefit. FDA often assesses the magnitude of benefit along a scale, according to specific endpoints or criteria, or by evaluating whether a pre-identified health threshold was achieved.

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The third measure of benefit is the probability of the patient experiencing one or more benefits. Based on the data provided, does the study predict which patients will experience a benefit or the probability that a patient will experience a benefit? It is important to understand the variation in public health benefits for different subgroups because these subgroups may experience different benefits or different levels of the same benefit.

The final measure of benefit is the duration of its effect. A treatment whose benefit lasts longer is more desirable than a treatment that must be repeated to preserve the benefit.

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The "Risk" factors in the benefit-risk determination include the severity, types, number and rates of harmful events; the probability of a harmful event; the duration of each harmful event; and the risk from false positive or false negative results, as in the case of diagnostic devices. These factors are considered individually and in the aggregate.

The first factor is the severity, types, number and rates of harmful events. This factor refers to events that result directly from the patient's use of the device. Examples of questions considered by the reviewer include: what are the device-related serious adverse events? What are the device-related non-serious adverse events? And, what other complications might a patient be subjected to as a result of a particular procedure?

The second risk factor is the probability that a harmful event will occur. This factor considers the probability of a patient experiencing a harmful event. Reviewers also consider whether patients are willing to accept the probable risk of a harmful event in exchange for a potential benefit.

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The third measure of risk is the duration of any harmful events - Questions include: How long does the harmful event last?
And… What type of intervention is required to address the harmful event?

Finally, in assessing the benefit-risk of diagnostic devices, reviewers consider the risk of false-positive or false-negative results. If a diagnostic device gives a false-positive result, a patient might receive an unnecessary treatment and incur unnecessary risks. If a diagnostic device gives a false-negative result, the patient might not receive a needed treatment and may miss out on the benefits of that treatment. Understanding the consequences of false positive and false negative results helps inform the benefit-risk determination of diagnostic devices.

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The guidance document specifies 7 additional factors that FDA considers while weighing the probable benefits and risks for medical devices. These factors are:
1) the uncertainty in the benefits and the risks,

2) characterization of the disease,

3) patient tolerance for risk and perspective on their benefit,

4) the availability of alternative treatments or diagnostics,

5) any risk mitigation strategies available,

6) the possibility of obtaining post-market data that improves the information about device outcomes, and

7) whether a device represents a novel technology that addresses an unmet medical need.

The first factor is the assessment of uncertainty. In assessing this factor, FDA reviewers consider variables such as study design, conduct of clinical trials, analysis of data, and reliability of the study outcomes. The repeatability of study results and how well a study can be generalized to a certain population can also influence the level of certainty. This factor also considers the probability of a patient in the intended population benefiting from the device or incurring risks.

The second factor is the characterization of the disease. In assessing this factor, FDA reviewers evaluate the clinical manifestation of the disease, how the disease affects patients, the potential for treating the condition, and the prognosis.

The third factor is patient tolerance for risk and perspective on the benefit. In assessing this factor, FDA reviewers evaluate data on how well patients tolerate the risks posed by a device. FDA recognizes that a patient-centric assessment of risk may reveal patients who are willing to tolerate a very high level of risk to achieve a probable benefit, especially if that benefit results in an improved quality of life. In this assessment, FDA considers evidence with respect to patients' perspectives on what constitutes sufficient benefits, as some groups of patients may value a benefit more than others.

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The 4th factor that FDA considers when making benefit-risk determinations is the availability of alternative treatments or diagnostics. FDA takes into account how effective these other treatments are and the risks they pose to patients.

The 5th factor is the use of risk mitigation strategies. These strategies, when appropriate, can minimize the probability of a harmful event from taking place. The reviewer will determine if the sponsor has identified ways to mitigate risks, for example through product labeling or educational programs. For in vitro diagnostics, risks may be mitigated by the use of complementary diagnostic tests.

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When looking at the next factor, postmarket data, FDA reviewers may consider if other devices with similar indications are on the market, and, if so, are the probabilities of benefits and risks similar to the device under review. They may consider if there are postmarket data that change the benefit-risk profile for devices already on the market. And reviewers may consider whether any data could be appropriately deferred to the postmarket setting, instead of required in the premarket setting.

The final factor in the assessment of benefit and risk is the consideration of whether a device includes breakthrough technologies or addresses an unmet medical need. In some circumstances, in order to facilitate patient access to new devices important for public health and to encourage innovation, we may tolerate greater uncertainty in an assessment of benefit or risk than for more established technologies. This factor takes into consideration how well a medical need is currently met with available therapies and how desirable the device is to patients.

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We anticipate this guidance document will primarily impact FDA Review Staff. However, through this guidance document, we hope that Industry will better understand the factors FDA considers when assessing benefit and risk during the premarket review process.

FDA Reviewers will receive education and training to help them systematically implement the tools and methods for conducting benefit-risk determinations during premarket review.

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I'd like to conclude with several closing remarks.

First, this guidance document has been developed to provide greater clarity for FDA Review Staff and Industry regarding the prominent factors FDA considers when making benefit-risk determinations during the premarket review process.

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Next, we recognize that the weighing of probable benefits against possible risks is an essential part of FDA's determination of a reasonable assurance of safety and effectiveness.

Finally, FDA wishes to highlight that this guidance document, with its examples and the worksheet attached, is intended to improve the predictability, consistency, and transparency of the premarket review process.

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We would like to answer a few questions you may have about how the guidance will impact your current and future premarket review submissions.

Question: When will this guidance be implemented? Answer: This guidance will be effective for all PMA applications and de novo petition decisions made beginning May 1, 2012.

Question: Will submissions received prior to May 1, 2012 be evaluated using the guidance?

Answer: They may, depending on how far along in the review process they are. The guidance document and the criteria within will be implemented beginning May 1, 2012.

Question: Will industry be required to fill out the attached worksheet?
Answer: No. The worksheet and examples provided in the guidance are designed to clarify what FDA reviewers consider when making benefit-risk determinations.

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For assistance with interpretation of this guidance document, please contact Dr. Randall Brockman, Acting Chief Medical Officer in ODE, or Dr. Robert Becker, Medical Officer and Team Leader in OIVD, at their respective email addresses listed on this companion slide.

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You can obtain a copy of this guidance document at the website on the screen. We thank you for participating in this CDRH Learn module, and encourage you to explore other modules, which you may find at www.fda.gov.

We thank you for your attention.

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