



CDRH Learn

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Guidance for Industry and FDA Staff:

Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications

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Purpose

- To identify and clarify the factors FDA considers when making benefit-risk determinations in PMA and *de novo* classification petitions
- To facilitate transparency, consistency, & predictability of the premarket review process for benefit-risk assessments



Background

- §513(a) of the Federal Food, Drug & Cosmetic Act
 - FDA determines if PMA applications provide “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,” among other relevant factors
 - FDA reviews valid scientific evidence to determine if data support claims made by Sponsor
 - Clinical data
 - Non-clinical data
 - Intended use/Indications for Use
 - For *de novo* classification petitions [513(f)(2)], FDA carefully considers a device’s risk profile in order to make a classification determination for the device under section 513(a)(1) of the FD&C Act; these could serve as predicates



Scope of Guidance

- Submission types impacted:
 - PMA applications
 - *de novo* classification petitions
- Device types impacted:
 - Therapeutic
 - Diagnostic



Development Process

- Contributing Team:
 - Benefit-risk working group from CDRH
- Chronology of Key Milestones:
 - August 2011: Draft issued for public comment
 - November 15, 2011: Docket closed
 - Final published on March 27, 2012
 - Implementation will begin May 1, 2012



Content of Guidance

- Addresses factors FDA considers important as part of the benefit-risk determination
- Provides examples of how FDA uses the factors in making benefit-risk determinations
- Includes worksheet, which reviewers will use in making benefit-risk determinations as part of the premarket process



Factors FDA Considers When Making Benefit-Risk Determinations



Factors FDA Considers When Making Benefit-Risk (B-R) Determinations

- Factors that characterize benefit
- Factors associated with risks
- Additional factors to be considered



Benefit factors in B-R determinations

- **Type of benefit**
 - What primary endpoints or surrogate endpoints were evaluated?
 - What is the public health impact of the device?
- **Magnitude of the benefit(s)**
 - Benefit assessed along a scale or according to specific endpoints or criteria
 - Pre-identified health threshold was achieved



Benefit factors in B-R determinations (Cont'd)

- **Probability of experiencing one or more benefit(s)**
 - Was the study able to predict which patients will experience a benefit?
 - What is the probability that a patient will experience the benefit?
 - Was there a variation in public health benefit for different populations?
- **Duration of effect**
 - A treatment whose benefit lasts longer is more desirable than a treatment that must be repeated.



Risk factors in B-R determinations

- **Severity, types, number and rates of harmful events**
 - What are the device-related serious adverse events?
 - What are the device-related non-serious adverse events?
 - What other procedure-related complications may a patient be subject to?
- **Probability of harmful event**
 - What percent of the intended patient population would expect to experience a harmful event?
 - Are patients willing to accept the probable risk of the harmful event, in exchange for potential benefits of the device?



Risk factors in B-R determinations (Cont'd)

- **Duration of harmful events**
 - How long does the harmful event last?
 - What type of intervention is required to address the harmful event?
- **Risk from false-positive or false-negative results for diagnostics**
 - What are the consequences of a false positive?
 - What are the consequences of a false negative?



Other Factors in B-R Determinations

- **Uncertainty**
 - How robust were the data? Are study results repeatable?
 - What is the probability that a patient in the intended population will receive a benefit or incur a risk?
- **Characterization of the disease**
 - How does the disease affect the patients?
 - Is the condition treatable?
- **Patient tolerance for risk/Their perspective on the benefit**
 - Would patients tolerate the risks in exchange for a benefit?
 - How much do patients value this treatment?



Other Factors in B-R Determinations (Cont'd)

- **Availability of alternative treatments or diagnostics**
 - What other therapies exist?
 - How effective are the alternative treatments?
- **Risk mitigation**
 - Has the Sponsor identified ways to mitigate risks, such as product labeling, education programs, complementary testing, etc?



Other Factors in B-R Determinations (Cont'd)

- **Postmarket data**
 - Are there other devices with similar indications on the market? Are the probabilities for effectiveness and rates of harmful events from those devices similar to what is expected for the device under review?
 - Is postmarket data available that changes the benefit-risk evaluation from what was available when the previous devices were evaluated?
 - Is there data that otherwise would be provided to support approval that could be deferred to the postmarket setting?
- **Novelty of technology addressing an unmet medical need**
 - How well is the medical need this device addresses being met by currently available therapies?
 - How desirable is this device to patients?



Impact

- Impact on Industry:
 - Industry will understand the factors FDA considers in analyzing risk and benefit during the premarket review process
- Impact on FDA Review Staff:
 - FDA Reviewers will utilize more consistent and transparent methods in conducting premarket reviews of risk and benefit



Conclusions

- Provides greater clarity for FDA reviewers and Industry regarding the prominent factors FDA considers when making benefit-risk determinations during the premarket review process



Conclusions

- An essential part of FDA's determination that there are reasonable assurances of safety and effectiveness is considering whether probable benefits outweigh probable risks
- Improves predictability, consistency, and transparency of the premarket review process



Questions and Answers

- **When will the guidance be implemented?**

This guidance will be effective for all PMA application and de novo petition recommendations made beginning May 1, 2012.

- **Will submissions received prior to May 1, 2012 be evaluated using the guidance?**

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.

- **Will Industry be required to fill out the attached worksheet?**

No. The worksheet and examples provided are present to clarify what CDRH reviewers consider when making benefit-risk determinations.



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Links

Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and *De Novo* Classifications

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM296379.pdf>

CDRH Learn:

www.fda.gov/Training/CDRHLearn/default.htm