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Consideration of Uncertainty in Making Benefit-Risk Determinations in Medical Device Premarket Approvals, De Novo Classifications and Humanitarian Device Exemptions - Final Guidance

Pablo Morales

Chief Medical Officer

Division of Circulatory Support, Structural and Vascular Devices

Office of Cardiovascular Devices

Office of Product Evaluation and Quality

Charles Viviano, MD, PhD

Deputy Office Director/Medical Officer

Office of Gastrorenal, ObGyn, General Hospital and Urology Devices

Office of Product Evaluation and Quality

Center for Devices and Radiological Health

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Agenda

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- CDRH's Benefit-Risk Guidances
- Uncertainty and Benefit-Risk
- Scope of the Guidance
- Factors When Considering Uncertainty in Benefit-Risk Determinations
- Application: Breakthrough Devices Subject to PMA
- Mitigations for Greater Uncertainty
- Application: Devices for Small Patient Populations Subject to PMA
- Examples
- Resources and Questions

Objectives



- Understand how uncertainty fits within the FDA's Benefit-Risk Framework
- Understand the factors the FDA considers in assessing the appropriate extent of uncertainty about a device's benefits and risks
- Understand how these factors are applied
 - Breakthrough Devices
 - Devices for Small Populations

Background

- The “Uncertainty Guidance” supplements existing Benefit-Risk Guidance Documents and Policies
- Provides further clarity on factors to consider related to uncertainty in benefit-risk determinations
- Outlines a rigorous, methodical approach for the consideration of uncertainty

Background

- Focuses on the balance between acceptable uncertainty in the premarket setting and postmarket setting
- The appropriate extent of uncertainty used in benefit-risk determinations to support premarket decisions is flexible and depends on multiple varying factors
- Provides a framework for determining what data collection is appropriate at the right time (for example, premarket vs. postmarket)

CDRH's Benefit-Risk Guidances

- [Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications](#)
- [Benefit-Risk Factors to Consider When Determining Substantial Equivalence in Premarket Notifications \(510\(k\)\) with Different Technological Characteristics](#)
- [Factors to Consider When Making Benefit-Risk Determinations for Medical Device Investigational Device Exemptions](#)
- [Factors to Consider Regarding Benefit-Risk in Medical Device Product Availability, Compliance, and Enforcement Decisions](#)

Uncertainty and Benefit-Risk



- The FDA considers the totality of evidence regarding the extent of probable benefits and extent of probable risks of a device, **including the extent of uncertainty in the benefit-risk information**
- The FDA also considers the appropriateness of risk mitigations and the collection of postmarket data **to address uncertainty in benefit-risk information**

Uncertainty and Benefit-Risk (Cont'd)



- There can be uncertainty around the type, magnitude, duration, frequency, and other aspects of a device's benefits and risks to patients

Uncertainty and Benefit-Risk (Cont'd)



“This guidance recognizes that to meet FDA’s mission to promote the public health in light of inherent uncertainties involved in the provision of medical care, it is important to **acknowledge and appropriately address uncertainty** in benefit-risk determinations supporting certain FDA premarket decisions, based on the factors outlined below and the specific context.”

Scope of the Guidance

- Applies to the FDA's consideration of uncertainty in benefit-risk determinations for Premarket Approval Applications (PMA), De Novo requests, and Humanitarian Device Exemption (HDE) applications
 - Examples include PMAs for Breakthrough Devices and PMAs for devices intended for small patient populations

Factors When Considering Uncertainty in Benefit-Risk Determinations

- The appropriate extent of uncertainty in benefit-risk determinations to support premarket decisions is flexible and depends on multiple varying factors.
- The balance between the appropriate extent of uncertainty in the premarket setting, relative to a product's probable benefits and risks – and, in turn, how much reliance the FDA can place on postmarket follow-up studies – is determined by these factors.

Factors When Considering Uncertainty in Benefit-Risk Determinations (Cont'd)



- The extent of the probable benefits of the device, taking into account the type, magnitude, probability, duration, and frequency of those benefits, including if the probable benefits are greater than those of approved or cleared alternative treatments or diagnostics or the standard of care



Factors When Considering Uncertainty in Benefit-Risk Determinations (Cont'd)

- The extent of the probable risks of the device, taking into account the severity, type, number, rates, probability, and duration of those risks, including if the probable risks are less than those of approved or cleared alternative treatments or diagnostics or the standard of care



Factors When Considering Uncertainty in Benefit-Risk Determinations (Cont'd)

- The extent of uncertainty regarding the benefit-risk profile of approved or cleared alternative treatments or diagnostics or the standard of care (for example., the strength of the evidence supporting the alternative treatment or diagnostic)



Factors When Considering Uncertainty in Benefit-Risk Determinations (Cont'd)

- Patients' perspective on appropriate uncertainty about the probable benefits and risks of the device, if available
- See the FDA's Guidance [Patient Preference Information - Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and De Novo Requests, and Inclusion in Decision Summaries and Device Labeling](#)



Factors When Considering Uncertainty in Benefit-Risk Determinations (Cont'd)

- The extent of the public health need (for example, seriousness of the illness; benefit-risk profile of other available therapeutics or diagnostics, if any, including the current standard of care; the portion of the target population for whom there would be a positive benefit-risk profile)



Factors When Considering Uncertainty in Benefit-Risk Determinations (Cont'd)

- The feasibility of generating extensive clinical evidence premarket based on appropriate considerations (for example, taking into account the prevalence of the disease or condition)



Factors When Considering Uncertainty in Benefit-Risk Determinations (Cont'd)

- The ability to reduce or resolve remaining uncertainty of a device's benefit-risk profile postmarket (for example, consideration of the FDA's authority to require postmarket data collection and the likelihood that the necessary postmarket data collection will be completed within reasonable timeframes)



Factors When Considering Uncertainty in Benefit-Risk Determinations (Cont'd)

- The likely effectiveness of mitigations, such as labeling, and other tools to help provide a reasonable assurance of safety and effectiveness of the device, as applicable



Factors When Considering Uncertainty in Benefit-Risk Determinations (Cont'd)

- The type of decision being made (for example, there is generally likely to be more uncertainty surrounding a device's benefit-risk profile based on the evidence submitted in an HDE application, as compared to a PMA, because the standards for approval are different)



Factors When Considering Uncertainty in Benefit-Risk Determinations (Cont'd)

- The probable benefits of earlier patient access to the device
- The FDA's consideration of these factors should be consistent with the FDA's statutory and regulatory authorities and requirements

Application: Breakthrough Devices Subject to PMA

- Breakthrough Devices, by their nature, generally have the potential to address unmet needs in serious conditions, and patients generally may be more willing to accept greater uncertainty in benefits and risks with respect to such products
- **To meet the statutory standards for approval, including that the device's probable benefits outweigh its probable risks, the FDA may accept greater uncertainty regarding the device's probable benefits and risks, when appropriate, because of the greater probable public health benefits of earlier patient access**

Application: Breakthrough Devices Subject to PMA (Cont'd)



- If greater uncertainty is deemed appropriate, certain postmarket controls might be necessary:
 - Timely postmarket data collection
 - Transparency
 - Accountability

Mitigations for Greater Uncertainty

○ Timely Postmarket Data Collection

- Require a postmarket study as a condition of approval within a specific, appropriate timeframe
- Ensure the FDA expectations are explicit in 522 orders and PMA/HDE conditions of approval

○ Transparency

- Labeling to describe when postmarket data collection is required to address greater uncertainty
- Include this info in the Summary of Safety and Effectiveness (SSED), Summary of Safety and Probable Benefit (SSPB), or De Novo Transparency Summary



Mitigations for Greater Uncertainty (Cont'd)

○ Accountability

- Hold an advisory committee meeting: If we have questions about whether postmarket data continues to support a reasonable assurance of safety and effectiveness
- Taking into account committee recommendation and postmarket data, consider issuing a withdrawal order or certain restrictions on sale/distribution or narrow indications for use

Application: Devices for Small Patient Populations Subject to PMA

- Because of the rarity of the disease or condition, it is generally infeasible or highly resource or time intensive to generate extensive clinical evidence premarket, and
- There is an unmet medical need that is addressed by the device, such as there are no available therapeutics or diagnostics for that patient population



Application: Devices for Small Patient Populations Subject to PMA (Cont'd)

- When not eligible for Breakthrough or HDE status
- While there is not a specific number of patients that would be considered a “small patient population,” this approach could be used for patients with a rare disease or condition or for patients within a clinically meaningful subset of a broader population



Example 1: Breakthrough Devices - PMA

DEVICE: Breakthrough Device intended to treat a currently treatment-resistant condition

PERFORMANCE GOAL = 70% in a proposed premarket single arm study

Assess for “conventional,” modest, and high extent of uncertainty in the clinical trial reflected by the one-sided significance level manifest by difference in sample size with implementation of appropriate postmarket controls

Example 1: Breakthrough Devices – PMA (Cont'd)

SCENARIO 1 – CONVENTIONAL UNCERTAINTY

Based upon Factors above and other relevant information, the FDA is not willing to accept additional uncertainty in premarket study design

- 1-sided significance = 2.5%
- Observed Performance Goal (PG) = 74%
- Expect sample size = **535** subjects to be 97.5% confident the PG is above 70%

Example 1: Breakthrough Devices - PMA (Cont'd)

SCENARIO 2 – MODEST UNCERTAINTY

Based upon Factors above and other relevant information, the FDA is willing to accept additional modest uncertainty in premarket study design with resulting modest pre- to postmarket shift

- 1-sided significance = 5%
- Observed Performance Goal = 74%
- Expect sample size = **385** subjects to be 95% confident the PG is above 70%
- “Modest” postmarket study as Condition of Approval, noted on website

Example 1: Breakthrough Devices - PMA (Cont'd)

SCENARIO 3 – HIGH UNCERTAINTY

Based upon Factors above and other relevant information, the FDA is willing to accept additional high uncertainty in premarket study design with significant pre- to postmarket shift

- 1-sided significance = 20%
- Observed Performance Goal = 74%
- Expect sample size = **125** subjects to be 80% confident the PG is above 70%
- Robust postmarket study with reliable source (for example., registry) to assure data collection
- Condition of Approval that postmarket study noted in labeling, Summary of Safety and Effectiveness (SSED), and on website, as appropriate



Example 2: Devices for Small Patient Populations – PMA

DEVICE: Intended to treat a disease with incidence of 10,000 new cases annually

- Not a Breakthrough Device, because the disease is not life-threatening or irreversibly debilitating
- Indicated disease is serious
- No available therapies
- Acceptable Performance Goal = 60%



Example 2: Devices for Small Patient Populations - PMA (Cont'd)

SCENARIO 1 – CONVENTIONAL UNCERTAINTY

Based upon Factors above and other relevant information, the FDA is not willing to accept additional uncertainty in premarket study design

- 1-sided significance = 2.5%
- Observed Performance Goal = 66%
- Expect sample size = **274** subjects to be 97.5% confident the Performance Goal is above 60%

Example 2: Devices for Small Patient Populations- PMA (Cont'd)

SCENARIO 2 – MODEST UNCERTAINTY

Based upon Factors above and other relevant information (patient recruitment would be challenging and a conventional premarket study appears infeasible), the FDA is willing to accept additional modest uncertainty in premarket study design with resulting modest pre- to postmarket shift

- 1-sided significance = 10%
- Observed Performance Goal = 66%
- Expect sample size = **128** subjects to be 90% confident the Performance Goal is above 60%
- “Modest” postmarket study as Condition of Approval, noted on website

Example 2: Devices for Small Patient Populations- PMA (Cont'd)

SCENARIO 3 – HIGH UNCERTAINTY

Based upon Factors above, relevant information above, and there is a reliable source of postmarket data (for example., registry), the FDA is willing to accept additional high uncertainty in premarket study design with significant pre- to postmarket shift

- 1-sided significance = 20%
- Observed Performance Goal = 66%
- Expect sample size = **65** subjects to be 80% confident the Performance Goal is above 60%
- Robust postmarket study with reliable source (for example., registry) to assure data collection
- Condition of Approval that postmarket study noted in labeling, Summary of Safety and Effectiveness (SSED), and on website, as appropriate

Resources

- [Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications](#), issued August 30, 2019
- [Benefit-Risk Factors to Consider When Determining Substantial Equivalence in Premarket Notifications \(510\(k\)\) with Different Technological Characteristics](#), issued on September 25, 2018
- [Factors to Consider When Making Benefit-Risk Determinations for Medical Device Investigational Device Exemptions](#), issued on January 13, 2017
- [Factors to Consider Regarding Benefit-Risk in Medical Device Product Availability, Compliance, and Enforcement Decisions](#), issued on December 27, 2016



Questions?

Division of Industry and Consumer Education:
DICE@fda.hhs.gov

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Under Heading: How to Study and Market Your
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