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

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Guidance for Industry and Food and Drug Administration Staff

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Preface

Public Comment

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Guidance for Industry and Food and Drug Administration Staff

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I. Introduction

This guidance document describes the Food and Drug Administration's (FDA or Agency) current approach to considering uncertainty in making benefit-risk determinations to support FDA premarket decisions for medical device premarket approval applications (PMAs), De Novo requests, and humanitarian device exemption (HDE) applications.[1] FDA believes the approach described in this guidance promotes the public health by helping patients have timely access to new medical devices meeting the applicable statutory standard for safety and effectiveness, such that probable benefits of device use outweigh the probable risks and the device will provide clinically significant results in a significant portion of the target population, based on the totality of the valid scientific evidence.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance means that something is suggested or recommended, but not required.

[1] FDA has also issued several guidance documents discussing benefit-risk determinations in various contexts (identified in note 17 below), including 510(k) notification and investigational device exemption (IDE) submissions, and those are not addressed in this guidance document.

II. Background

The 1976 Medical Device Amendments (Public Law 94-295) to the Federal Food, Drug, and Cosmetic Act (FD&C Act) established a risk-based framework for the regulation of medical devices. The law established a three-tiered risk classification system based on the risk posed to patients should the device fail to perform as intended. Under this system, devices that pose greater risks to patients are subject to more regulatory controls and requirements. Specifically, general controls are sufficient to provide reasonable assurance of a Class I device's safety and effectiveness,[2] while special controls are utilized for Class II devices for which general controls alone are insufficient to provide reasonable assurance of device safety and effectiveness.[3] The FDA classifies into Class III devices intended to be used in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health, or that may present a potential unreasonable risk of illness or injury, and for which insufficient information exists to determine that general controls and special controls are sufficient to provide reasonable assurance of the safety and effectiveness of a device.[4] This highest-risk class of devices is subject to premarket approval to demonstrate a reasonable assurance of safety and effectiveness.[5] Even for this highest-risk class of devices, the evidence FDA requires for premarket approval has long been flexible and tailored to the device. Thus, the evidence to support this determination may well vary according to the characteristics of the device, its conditions of use, the existence and adequacy of warnings and other restrictions, among other factors.[6] Additionally, in determining the safety and effectiveness of a device, FDA considers, among other relevant factors, the population of use, the conditions of use, the probable benefits to health weighed against any probable injury or illness, and the reliability of the device.[7] There is generally more flexibility in the amount of clinical evidence needed for devices than for drugs and biological products, because they are subject to different statutory criteria. In addition, the mechanism of action and modes of failure are generally more predictable and better understood for devices than for drugs and biological products. Further, the design process for a device is more often an iterative process based largely on rational design and non-clinical testing rather than clinical studies.

Since 1976, Congress has repeatedly expanded the mandate of FDA, broadening its mission, making its focus more patient-centric, and making the regulatory paradigms it applies more flexible. For example, in the Food and Drug Administration Modernization Act of 1997 (FDAMA) (Public Law 105-115), Congress expanded FDA's mission from "to protect public health" to include "to promote public health."[8] The Agency has interpreted the latter to include

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[2] *See* section 513(a)(1)(A) of the FD&C Act (21 U.S.C. § 360c(a)(1)(A)).
[3] *See* section 513(a)(1)(B) of the FD&C Act (21 U.S.C. § 360c(a)(1)(B)). Special controls were added to the FD&C Act through the Safe Medical Devices Act of 1990 (Public Law 101-629).
[4] *See* section 513(a)(1)(C) of the FD&C Act (21 U.S.C. § 360c(a)(1)(C)).
[5] *See, e.g.,* section 513(a)(1)(C) of the FD&C Act (21 U.S.C. § 360c(a)(1)(C)).
[6] *See* 21 CFR 860.7.
[7] *See* 21 CFR 860.7(b)(1)
[8] Specifically, FDA's mission includes "protect[ing] the public health by ensuring that…there is reasonable assurance of the safety and effectiveness of devices intended for human use" and "promot[ing] the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner." Section 1003 of the FD&C Act (21 U.S.C. § 393).

fostering medical device innovation and facilitating timely patient access to high quality, safe and effective medical devices. In that same legislation, Congress enacted what have been called the "least burdensome" provisions for medical devices, to ensure that FDA only requests information that is necessary to make substantial equivalence determinations for 510(k)s[9] and to establish device effectiveness for PMAs.[10] In addition, for PMAs, FDA must consider, in consultation with the applicant, the least burdensome appropriate means of evaluating device effectiveness.[11] The original least burdensome provisions also included the requirement that the FDA shall consider whether the extent of data that otherwise would be required for approval of the PMA with respect to effectiveness can be reduced through reliance on postmarket controls.[12]

Congress expanded the least burdensome provisions of the FD&C Act through the Food and Drug Administration Safety and Innovation Act (FDASIA) (Public Law 112-144) and the 21st Century Cures Act (Cures Act) (Public Law 114-255).[13] For example, section 515(c)(5)(C) of the FD&C Act (21 U.S.C. § 360e(c)(5)(C)), as added by the Cures Act, requires FDA to "consider the role of postmarket information in determining the least burdensome means of demonstrating a reasonable assurance of device safety and effectiveness" for PMAs. The least burdensome provisions do not, however, alter the applicable regulatory standards for marketing authorizations.[14] FDA describes the guiding principles and approach for the consistent application of least burdensome principles throughout the medical device total product lifecycle in the Guidance The Least Burdensome Provisions: Concept and Principles.[15]

The Agency generally provides marketing authorization for a device when it meets the applicable standards, including that its benefits outweigh its risks. For example, section 513(a)(2) of the FD&C Act (21 U.S.C. § 360c(a)(2)) states that safety and effectiveness of a device under a PMA are to be determined in part by "weighing any probable benefits to health from the use of the device against any probable risk of injury or illness from such use."[16] The extent of

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[9] *See* section 513(i)(1)(D) of the FD&C Act (21 U.S.C. § 360c(i)(1)(D)).
[10] *See* section 513(a)(3)(D)(ii) of the FD&C Act (21 U.S.C. § 360c(a)(3)(D)(ii)).
[11] *Id.*
[12] *See* section 513(a)(3)(C) of the FD&C Act (21 U.S.C. § 360c(a)(3)(C)).
[13] *See* the additional least burdensome provisions of the FD&C Act, sections 513(i)(1)(D)(ii) – (iii), 513(a)(3)(D)(iii) – (iv), and 515(c)(5)(A) – (D) (21 U.S.C. §§ 360c(i)(1)(D)(ii)-(iii), 360c(a)(3)(D)(iii)-(iv), and 360e(c)(5)(A) - (D)).
[14] *See* sections 513(a)(3)(D)(iv), 513(i)(1)(D)(iii), and 515(c)(5)(D) of the FD&C Act (21 U.S.C. §§ 360c(a)(3)(D)(iv), 360c(i)(1)(D)(iii), and 360e(c)(5)(D)).
[15] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/least-burdensome-provisions-concept-and-principles.
[16] Further, FDA regulation in 21 CFR 860.7(d)(1) states that there is a reasonable assurance that a device is safe "when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks." For further information about device effectiveness, see section 513(a)(3) of the FD&C Act (21 U.S.C. § 360c(a)(3)) (states that effectiveness is to be determined based on well-controlled investigations or other valid scientific evidence from which "it can fairly and responsibly be concluded by qualified experts that the device will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling of the device") and 21 CFR 860.7(e)(1) (states that there is a reasonable assurance that a device is effective "when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results").

uncertainty of the benefits and risks of a device is a factor we consider when making the benefit-risk determination that is part of the evaluation of a device in a variety of contexts, including for PMA approvals, De Novo classifications, 510(k) clearances, HDE approvals, and IDE approvals. For example, FDA's final guidance on Factors to Consider in Making Benefit-Risk Determinations in Medical Device Premarket Approval and *De Novo* Classifications ("PMA and De Novo Benefit-Risk guidance")[17] includes consideration of patient preference and uncertainty in the process of making such determinations and provides a framework for benefit-risk decision-making for these submissions. To better articulate FDA's policy on its decision-making in various other contexts across the total product lifecycle, including with respect to other types of submissions for devices, FDA has published several guidances that demonstrate a flexible, patient-centric, benefit-risk approach, including the consideration of patient preferences and uncertainty.[18] These guidances, including this Uncertainty guidance, complement one another: for example, the PMA and De Novo Benefit-Risk guidance lists uncertainty as a factor in benefit-risk decisions, while this guidance further clarifies how we determine the appropriate extent of uncertainty for a device. FDA's approach is tailored to the type and intended use of the device and the type of decision we are making. For example, as a general matter, high-risk and innovative moderate-risk devices will typically need clinical evidence to show reasonable assurance of safety and effectiveness, including that the benefits of the device outweigh its risks.[19] However, non-clinical performance data, such as bench studies, studies in animals,[20] and/or computational modeling studies can also provide essential information on the safety and effectiveness of a device (including its principles of operation, as well as potential failure or

[17] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/factors-consider-when-making-benefit-risk-determinations-medical-device-premarket-approval-and-de.

[18] *See, e.g.*, Factors to Consider When Making Benefit-Risk Determinations for Medical Device Investigational Device Exemptions (available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/factors-consider-when-making-benefit-risk-determinations-medical-device-investigational-device); Benefit-Risk Factors to Consider When Determining Substantial Equivalence in Premarket Notifications [510(k)] with Different Technological Characteristics (available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/benefit-risk-factors-consider-when-determining-substantial-equivalence-premarket-notifications-510k); Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies (available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/investigational-device-exemptions-ides-early-feasibility-medical-device-clinical-studies-including); Factors to Consider Regarding Benefit-Risk in Medical Device Product Availability, Compliance, and Enforcement Decisions (available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/factors-consider-regarding-benefit-risk-medical-device-product-availability-compliance-and); Qualification of Medical Device Development Tools (available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/qualification-medical-device-development-tools); and 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 (available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-preference-information-voluntary-submission-review-premarket-approval-applications).

[19] Most low-risk devices are exempt from FDA review before marketing, although manufacturers are still subject to certain requirements. Manufacturers of many moderate-risk devices may obtain marketing authorization by demonstrating that their devices are substantially equivalent to a legally marketed "predicate" device (e.g., a device already cleared by FDA), which can often be achieved through non-clinical testing.

[20] FDA supports the principles of the "3Rs," to reduce, refine, and replace animal use in testing when feasible. We encourage sponsors to consult with us if they wish to use a non-animal testing method they believe is suitable, adequate, validated, and feasible. We will consider if such an alternative method could be assessed for equivalency to an animal test method.

malfunction modes). That information can inform the clinical trial design and extent of premarket clinical evidence generation, as well as the extent of postmarket data that may be required.

In the HDE provisions in section 520(m) of the FD&C Act (21 U.S.C. § 360j(m)), first enacted in the Safe Medical Devices Act of 1990 (Public Law 101-629),[21] Congress incorporated greater uncertainty compared to PMAs. In the HDE provisions in section 520(m) of the FD&C Act, Congress provided that FDA may grant an exemption from the requirement to demonstrate a reasonable assurance of effectiveness for devices that meet certain criteria.[22] Therefore, when compared to a PMA or De Novo request, both of which require a demonstration of reasonable assurance of safety and effectiveness,[23] there is generally likely to be greater uncertainty surrounding the benefit-risk profile based on the evidence submitted in an HDE application. This exemption for humanitarian use devices implicitly acknowledges the challenges in generating sufficient clinical evidence to demonstrate a reasonable assurance of effectiveness when the patient population is very small.

In addition, Congress has required the application of particular controls, including profit limitations and the approval of an institutional review board before a device approved under an HDE can be used at a facility to treat or diagnose patients. However, some of these controls may have tempered interest in utilization of the HDE pathway by medical device sponsors, and Congress has scaled back some of the limitations.[24]

In 2015, following pilots conducted over four years, FDA established the Expedited Access Pathway (EAP) Program as a voluntary program for certain medical devices (e.g., devices that represent breakthrough technologies that provide a clinically meaningful advantage over existing legally marketed technologies) that address an unmet need in the treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions.[25] Under this EAP program, an eligible device subject to a PMA could be approved with greater uncertainty about the product's

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[21] The Safe Medical Devices Act was enacted on November 28, 1990, and section 520(m) was further amended by FDAMA (Public Law 105-115), the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law 110-85), FDASIA (Public Law 112-144), the Cures Act (Public Law 114-255), and the FDA Reauthorization Act of 2017 (FDARA) (Public Law 115-52).

[22] The HDE provisions specify that in order to grant an HDE, FDA must find, among other things, that "the device will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from the use of the device outweighs the risk of injury or illness from its use, taking into account the probable risks and benefits of currently available device[s] or alternative forms of treatment." Section 520(m)(2)(C) of the FD&C Act (21 U.S.C. § 360j(m)(2)(C)).

[23] The statutory standards for approval of a PMA include a showing of reasonable assurance that the device is safe and effective. See section 515(d) of the FD&C Act (21 U.S.C. § 360e(d)). The De Novo classification process is appropriate for devices that would otherwise be subject to PMA but for which general controls or general and special controls provide a reasonable assurance of safety and effectiveness. See section 513(f)(2) of the FD&C Act (21 U.S.C. § 360c(f)(2)).

[24] *See* the Safe Medical Devices Act of 1990 (Public Law 101-629) section 14, which added section 520(m) of the FD&C Act (21 U.S.C. § 360j(m)), and section 303 of FDAAA (Public Law 110-85), section 613 of FDASIA (Public Law 112-144), section 3052 of the Cures Act (Public Law 114-255), and section 502 of FDARA (Public Law 115-52), which further amended section 520(m) of the FD&C Act.

[25] The Breakthrough Devices Program, which FDA established under section 515B of the FD&C Act (21 U.S.C. § 360e-3) as added by the Cures Act and amended by FDARA, supersedes the Expedited Access Pathway Program.

benefits and risks, provided that, among other requirements, the data still support a reasonable assurance of safety and effectiveness, including that the probable benefits of the device outweighed its risks for a patient population with unmet medical needs. For devices subject to PMA, the Agency has the authority to impose, when warranted, postmarket requirements, including post-approval studies and postmarket surveillance, as a condition of approval, which could be used to address this greater uncertainty.[26] In the Breakthrough Device provisions of the FD&C Act, as added by the Cures Act and amended by the FDA Reauthorization Act of 2017 (FDARA), Congress codified and expanded this program to include 510(k) devices.[27] Similar to the least burdensome provisions, the Breakthrough Device provisions make clear that they do not alter the standards for substantial equivalence, premarket approval, or granting of a De Novo request.[28]

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. FDA also considers the appropriateness of risk mitigations and the collection of postmarket data to address the uncertainty in the benefit-risk information. FDA's decisions operate in the context of a broader healthcare system, where there is inherent uncertainty in the provision of health care, including uncertainty about how the general benefit-risk profile of a given medical product or procedure will translate to an individual patient's health outcome, differences in regional and local medical practice, and continually evolving standard of care.

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. This includes considering the applicable patient population's willingness to accept more uncertainty in a device's benefits and risks, particularly when there are no acceptable alternatives available. Furthermore, the continuous, robust generation of evidence throughout the premarket and postmarket setting as part of a learning health care system (which itself has inherent uncertainty in the generation of clinical evidence, e.g., due to limited sample size compared to the intended patient population and duration of clinical trials) is important to continuously refine our understanding of how medical devices are used and perform, and corresponding patient outcomes. This understanding within the broader healthcare system can inform FDA's regulatory decision-making regarding medical devices.

III. Scope

[26] *See* sections 513(a)(3)(C), 515(c)(5)(C), 515(d)(1)(B)(ii), and 515B(e)(2)(C) of the FD&C Act (21 U.S.C. §§ 360c(a)(3)(C), 360e(c)(5)(C), 360e(d)(1)(B)(ii), and 360e-3(e)(2)(C)); 21 CFR 814.82.

[27] *See* section 515B of the FD&C Act (21 U.S.C. § 360e-3), as created by section 3051 of the Cures Act (Public Law 114-255) and amended by section 901 of FDARA (Public Law 115-52). *See also* Breakthrough Devices Program (available at https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM581664.pdf).

[28] *See* section 515B(g) of the FD&C Act (21 U.S.C. § 360e-3(g)).

FDA has published several guidance documents on factors to consider in benefit-risk determinations for a variety of regulatory circumstances, including specific application types for medical devices.[29] The principles in this guidance apply to FDA's consideration of uncertainty in benefit-risk determinations for PMAs, De Novo requests, and HDE applications.[30] This guidance enhances transparency and consistency in the premarket review process by describing several factors that FDA considers in assessing the appropriate extent of uncertainty about a device's benefits and risks when reviewing these types of premarket submissions. Further, this guidance provides illustrative examples based on current practice of how the principles for considering uncertainty could be applied in the context of clinical evidence and when greater uncertainty could be appropriate in the PMA context, such as PMAs for Breakthrough Devices and PMAs for devices intended for small patient populations. However, these examples are not intended to imply that FDA's consideration of uncertainty in premarket benefit-risk determinations is limited to these scenarios.

The policies in the guidance further FDA's mission to promote the public health by fostering medical device innovation and facilitating timely patient access to high quality, safe and effective medical devices. In addition, the benefit-risk based framework described in this guidance aims to assure greater transparency, predictability, consistency, and efficiency, using least burdensome principles.

IV. Consideration of Uncertainty in Making Benefit-Risk Determinations to Support Certain Premarket Decisions

Generally, in premarket decision-making for devices, there exists some uncertainty around benefits and risks. There can be uncertainty around the type, magnitude, duration, frequency, and other aspects of a device's benefits and risks to patients. The statutory standard for medical devices, including for certain marketing authorizations, reflects this reality by requiring devices to have a "reasonable" assurance, rather than an absolute assurance, of safety and effectiveness.[31]

The appropriate extent of uncertainty regarding a device's benefits and risks depends on the type of premarket decision and its context. As a result, the appropriate uncertainty in a benefit-risk determination to support a device premarket decision would depend on the circumstances, including the totality of information about the device. In considering uncertainty in benefit-risk determinations, FDA considers several factors, as appropriate to the circumstances, including:

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[29] *See, e.g.*, Factors to Consider When Making Benefit-Risk Determinations for Medical Device Investigational Device Exemptions (available at https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm451440.pdf); and the PMA and De Novo Benefit-Risk guidance.

[30] FDA expects to apply benefit-risk determinations in a limited set of 510(k) clearance decisions. *See* Benefit-Risk Factors to Consider When Determining Substantial Equivalence in Premarket Notifications [510(k)] with Different Technological Characteristics (available at https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM404773.pdf).

[31] The "reasonable assurance of safety and effectiveness" standard can be found in section 513 of the FD&C Act (21 U.S.C. § 360c) and 21 CFR 860.7. We note that the standard for HDEs in section 520(m)(2)(C) of the FD&C Act (21 U.S.C. § 360j(m)(2)(C)) is different, but it too uses language that accepts uncertainty.

- The extent of the probable benefits of the device, taking into account the type, magnitude, probability, duration, and frequency of those benefits,[32] including if the probable benefits are greater than those of approved or cleared alternative treatments or diagnostics or the standard of care;

- The extent of the probable risks of the device, taking into account the severity, type, number, rates, probability, and duration of those risks,[33] including if the probable risks are less than those of approved or cleared alternative treatments or diagnostics or the standard of care;

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

- Patients' perspective on appropriate uncertainty about the probable benefits and risks of the device, if available;[34]

- The extent of the public health need (e.g., 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);

- The feasibility of generating extensive clinical evidence premarket based on appropriate considerations, e.g., taking into account the prevalence of the disease or condition;

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

- 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;

- The type of decision being made (e.g., there is generally likely to be more uncertainty surrounding a device's benefit-risk profile based on the evidence submitted in an

[32] For further discussion of type, magnitude, probability, and duration of benefits, see PMA and De Novo Benefit-Risk guidance.
[33] For further discussion of severity, type, number, rates, probability, and duration of risks, see PMA and De Novo Benefit-Risk guidance.
[34] *See* 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 (available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-preference-information-voluntary-submission-review-premarket-approval-applications).

HDE application, as compared to a PMA, because the standards for approval are different); and

- The probable benefits of earlier patient access to the device.

FDA's consideration of these factors is intended to be pragmatic, context-dependent (considered in the context of the relevant non-clinical and/or clinical information about the device, e.g., information about the device's mechanism of action and modes of failure), and consistent with FDA's statutory and regulatory authorities and requirements.

When considering a De Novo request, FDA expects that the risks associated with the device would contribute to its analysis of uncertainty and the overall benefit-risk profile, recognizing that the FDA may be able to accept greater uncertainty due to factors such as whether the device presents minimal risks or whether the imposition of special controls can mitigate the risks.

In some cases, resolving or reducing the extent of uncertainty postmarket may not be warranted. For example, the HDE pathway accepts greater uncertainty premarket because the FD&C Act does not require a demonstration of a reasonable assurance of effectiveness; further, the FD&C Act does not require data collection on device effectiveness postmarket.[35] Other cases may include, but are not limited to, cases where the extent of uncertainty is small, risks to patients are minimal, or where postmarket data collection is not feasible and other postmarket controls help to address uncertainty in the benefit-risk issues related to premarket authorization. In any case, the applicable marketing authorization standards under the FD&C Act and FDA regulations must be met.

V. Application: Breakthrough Devices and Devices for Small Populations, Subject to PMA

As noted above, two circumstances where greater uncertainty could be appropriate in the PMA context are Breakthrough Devices subject to PMA requirements and devices intended for small patient populations subject to PMA requirements. In this section, the guidance describes in more detail how FDA intends to apply the policies in this guidance to these two circumstances, and then gives examples providing simplistic illustrations of how the concepts in the guidance could be reflected in premarket study design and postmarket data collection. In any case, the decision as to whether or not such a device meets the statutory standard of reasonable assurance of safety and effectiveness for its intended use would be based on the totality of the valid scientific evidence, including clinical studies and non-clinical testing.[36]

A. Breakthrough Devices Subject to PMA

For many Breakthrough Devices[37] that are subject to a PMA, in determining that the statutory standards for approval have been met, including that the device's probable benefits outweigh its probable risks, FDA may accept greater uncertainty regarding the device's probable benefits and

[35] *See* section 520(m) of the FD&C Act (21 U.S.C. § 360j(m)). Note that devices approved through the HDE pathway are subject to certain profit and use restrictions. *See id*.
[36] *See* sections 513(a) and 515(d) of the FD&C Act (21 U.S.C. §§ 360c(a) and 360e(d)) and 21 CFR 860.7.
[37] The criteria for breakthrough devices are specified in 515B(b) of the FD&C Act (21 U.S.C. § 360e-3(b)).

risks, when appropriate, because of the greater probable public health benefits of earlier patient access. Further, it may be appropriate to collect additional data in the postmarket setting, rather than premarket, to address the greater uncertainty about the device's probable benefits and risks, provided that the statutory standards for premarket approval are met ("premarket-postmarket data shift"). This may depend, in part, on the magnitude of the probable public health benefit (e.g., a greater data shift could be appropriate if the probable magnitude of the benefit is high) and the likelihood that the data can and will be collected in a timely manner postmarket (e.g., a large data shift may not be appropriate if postmarket data collection is not likely to occur in a timely manner or at all).[38] For example, as a general matter, patient enrollment in device postmarket studies assessing approved indications has proven challenging, because patients do not need to participate in a clinical study to gain access to the technology. However, if there is a high likelihood that complete postmarket data will be collected in a timely fashion, FDA may accept greater uncertainty with respect to its premarket benefit-risk determination if appropriate under the circumstances. For Breakthrough Devices subject to PMA, FDA may also decide to utilize one or more of the postmarket controls described below.

FDA, working with the sponsor, intends to determine the appropriate uncertainty and the appropriate postmarket controls based on the specific circumstances and the factors outlined in Section IV. For example, if FDA determines that greater uncertainty is appropriate but that certain postmarket controls are necessary, a sponsor may take that approach, or provide additional data in the premarket setting that will reduce uncertainty, likely resulting in fewer postmarket controls. FDA recognizes that there may be different ways for sponsors to demonstrate reasonable assurance of safety and effectiveness and encourages sponsors to approach FDA early to discuss potential development programs.

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.[39] In addition, for devices subject to PMAs, FDA has the authority to establish postmarket controls, including postmarket data collection.[40] Accordingly, for PMAs for Breakthrough Devices, FDA may accept greater uncertainty if appropriate. In any case, the appropriate uncertainty for a given device will depend on the specifics of the situation. In addition, the postmarket controls described below could apply to non-Breakthrough Devices subject to PMA, depending on the circumstances.

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[38] *See* section 515B(e)(2)(C) of the FD&C Act (21 U.S.C. § 360e-3(e)(2)(C)).

[39] *See* Breakthrough Devices Program (available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/breakthrough-devices-program).

[40] *See* sections 513(a)(3)(C), 515(c)(5)(C), 515(d)(1)(B)(ii), and 515B(e)(2)(C) of the FD&C Act (21 U.S.C. §§ 360c(a)(3)(C), 360e(c)(5)(C), 360e(d)(1)(B)(ii), and 360e-3(e)(2)(C)); 21 CFR 814.82. Note also that if FDA finds that a Class II or Class III device is intended to be implanted for more than a year or is a life-sustaining or life-supporting device used outside a user facility, would be reasonably likely to have serious adverse health consequences if the device failed, or is expected to have significant use in pediatric populations, FDA may require postmarket surveillance by order under section 522 of the FD&C Act (21 U.S.C. § 360l). *See also* Postmarket Surveillance Under Section 522 of the Federal Food, Drug, and Cosmetic Act (available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/postmarket-surveillance-under-section-522-federal-food-drug-and-cosmetic-act).

(1) Timely Postmarket Data Collection

It is critical that data collected in the postmarket setting is reliable, high quality, and collected in a timely manner. Therefore, when FDA believes postmarket data collection is appropriate, such as part of a premarket-postmarket data shift, FDA intends to include timely submission of data from postmarket studies as a condition of approval. FDA already requires postmarket studies as a condition of approval to provide information on the continued reasonable assurance of safety and effectiveness of many approved medical devices. These postmarket studies are listed on the Agency's website.[41] FDA has authority to withdraw the approval of a PMA if conditions of approval, including the collection of postmarket data, are not met.[42] FDA intends to work with the sponsor to reach agreement on appropriate postmarket data collection.

However, challenges to timely and appropriate postmarket data collection have hampered the ability of FDA and sponsors to rely on postmarket data collection in some circumstances. For example, as previously noted, patients may have less incentive to enroll in postmarket studies when they can access the device without participating in a clinical study. Where there is a well-established postmarket data collection mechanism, such as a registry, the FDA and the sponsor have more confidence that the requisite postmarket data will be generated as planned. In such cases, when appropriate, the Agency would consider relying more on postmarket data collection. FDA encourages interested sponsors to explore the use of "real-world data"[43] sources so that there is more confidence in generating timely postmarket data and also to ensure that the sources that sponsors plan to use are sufficiently reliable and relevant.

For Breakthrough Devices, FDA may require, as a condition of approval, the collection of postmarket data within a specific, appropriate timeframe. Timely postmarket data collection and submission to FDA can be critical to provide patients with an assurance that the device remains reasonably safe and effective. Therefore, the Agency intends to enforce the specific timeframe on the collection of postmarket data that is included as a condition of approval under section 515(d)(1)(B)(ii) of the FD&C Act (21 U.S.C. § 360e(d)(1)(B)(ii)). Section 515B(e)(2)(C) of the FD&C Act (21 U.S.C. § 360e-3(e)(2)(C)) authorizes, when scientifically appropriate, the utilization of "timely" postmarket data collection to facilitate expedited and efficient development and review of Breakthrough Devices. The Agency intends to work with sponsors to determine a reasonable timeframe for the particular device in situations where postmarket data collection is considered to be appropriate and the least burdensome approach to allow for marketing authorization.

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[41] Available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm.

[42] *See* 21 CFR 814.46(a). Additionally, failure to comply with post approval requirements under 21 CFR 814.82(a)(2) may cause the device to be misbranded under section 502(t)(2) of the FD&C Act (21 U.S.C. § 352(t)(2)) and constitute a prohibited act under section 301(q)(1)(B) of the FD&C Act (21 U.S.C. § 331(q)(1)(B)), which could result in seizure, injunction, or other enforcement action.

[43] FDA defines Real-World Data (RWD) as data relating to patient health status and/or delivery of health care routinely collected from a variety of sources. RWD sources include registries. *See* Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices (available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-real-world-evidence-support-regulatory-decision-making-medical-devices).

(2) Transparency

In addition to including timely completion and submission of postmarket evidence for a device as a condition of approval, FDA can also include as a condition of approval that the device labeling include certain information, as appropriate.[44] Where postmarket data collection is required as a condition of approval to address greater uncertainty in the device's probable benefits and risks, FDA intends to consider whether it would be appropriate (e.g., whether it would be helpful to healthcare providers) to include as a condition of approval that the device labeling describe the postmarket data collection and its purpose.

Where applicable, FDA also intends to include such information in the Summary of Safety and Effectiveness Data (SSED) and to flag postmarket studies that are a condition of approval for the device on our website.[45] Sponsors are encouraged to work with FDA to accurately characterize the postmarket data collection and its purpose. When the additional postmarket data are provided, and FDA determines that the data are sufficient and continue to support the reasonable assurance of safety and effectiveness of the device, if applicable, FDA intends to make appropriate changes to the SSED and to inform the sponsor that the sponsor may make appropriate changes to the device's labeling to reflect the new information. This guidance does not alter the existing regulatory mechanism for effecting such changes.

(3) Accountability

When the sponsor submits postmarket data as a condition of approval and FDA has questions regarding whether the data continue to support a reasonable assurance of the device's safety and effectiveness, the Agency generally expects to hold an advisory committee meeting.

Generally, FDA intends to schedule the meeting in advance – for a time soon after the timeframe for submitting the postmarket evidence under the conditions of approval – and then cancel the meeting if it is unnecessary. When the Agency holds an advisory committee meeting, we intend to consider the recommendations of the advisory committee in determining whether the data continue to support a reasonable assurance of the device's safety and effectiveness, and in determining next steps, which could include issuing a withdrawal order or, if warranted by the data and agreed upon by the PMA holder, certain restrictions on the sale and distribution of the device or narrowing the device's indications for use.

FDA also intends to take appropriate administrative or enforcement action if a sponsor does not generate and submit the requisite postmarket data within the specified timeframe.[46]

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[44] *See* 21 CFR 814.82.

[45] FDA maintains a list of postapproval studies that are required as a condition of approval since 2005 for a PMA, Product Development Protocol, or HDE. *See* https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma_pas.cfm.

[46] For further discussion of administrative and enforcement actions in such contexts, see Balancing Premarket and Postmarket Data Collection for Devices Subject to Premarket Approval (available at https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm393994.pdf).

B. Devices for Small Patient Populations Subject to PMA

The FDA believes that the approach described above could be applied to some devices intended to treat or diagnose a small patient population, particularly where (1) 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 (2) 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. This approach could be applied when the device is not eligible for the Breakthrough Device Program (e.g., does not treat or diagnose a life-threatening or irreversibly debilitating disease or condition) or the HDE pathway (e.g., more than 8,000 individuals are affected annually). This would give the sponsors of eligible devices options for how they could meet the reasonable assurance of safety and effectiveness standard where greater uncertainty may be appropriate under the circumstances (e.g., smaller premarket data collection with larger postmarket data collection and other postmarket controls, greater premarket data collection with smaller postmarket data collection and no or fewer other postmarket controls, or even greater premarket data collection with no or little postmarket data collection and other postmarket controls). 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. This approach would be applied on a case by case basis, taking into account the factors described in Section IV and the relevant non-clinical and/or clinical information about the device. Sponsors may submit a Q-submission to discuss with the appropriate review team.[47]

C. Examples

The following hypothetical examples are solely intended to illustrate what the impact on the clinical trial size could be under different scenarios of uncertainty, taking into account the factors described in Section IV and the relevant non-clinical and/or clinical information about the device. However, the use of a particular fact pattern or a particular value of a clinical trial design parameter (such as p-value cutoff, one-sided significance level, level of confidence, credible or confidence interval, or posterior probability) is not intended to convey either FDA policy or a determination by FDA that such a fact pattern or the application of such a statistical decision threshold is acceptable in a given situation, and should not be used in isolation to inform the size of a clinical trial and its statistical analysis plan. Moreover, statistical measures, such as p-values, are not context-independent measures of the extent of uncertainty regarding a particular device's clinically significant benefits and risks. Although the examples below illustrate how uncertainty may be reflected in the confidence level or one-sided significance level for a clinical study, we note that uncertainty may be reflected in other ways, when appropriate, based on the circumstances, e.g., use of surrogate endpoints.

Finally, as noted above, the decision as to whether or not a device provides a reasonable assurance of safety and effectiveness is based on the totality of the valid scientific evidence, including clinical studies and non-clinical testing. The appropriate extent of uncertainty of benefits and risks in a given case will depend on consideration of the factors set forth in Section

[47] *See* Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program (available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program).

IV (e.g., the disease or condition at issue, the availability of alternative products, and risk mitigations) and other relevant information concerning the device. We anticipate that the greatest extent of uncertainty discussed in the examples below would only be appropriate under rare circumstances and, in any case, the sponsor must show, among other things, that the totality of the valid scientific evidence provides a reasonable assurance of safety and effectiveness of the device.[48]

(1) Breakthrough Devices – PMA

a. Breakthrough Treatment Device

Consider a Breakthrough Device intended to treat a currently treatment-resistant condition. Suppose FDA considers the benefit-risk factors of the device for this indication and the relevant non-clinical and/or clinical information, and determines that a performance goal of 70% of the treated patients experiencing treatment success is acceptable. Assume the proposed premarket clinical study for this case is a single arm study. If the lower confidence limit of the success rate estimate is greater than 70%, the endpoint would be met. The following three cases illustrate how there could be differences in sample sizes for the premarket clinical study where a "conventional," modest, and high extent of uncertainty – that is reflected in the one-sided significance level for the study – is appropriate under the circumstances, with implementation of appropriate postmarket controls, including postmarket data collection.

Case 1: Conventional Uncertainty

In this case, based on the considerations in Section IV and other relevant information, FDA determines that the one-sided significance level should be 2.5%. If the observed success rate is 74%, we would expect a study with a sample size of **535** patients to be 97.5% confident that the proportion of successful patients is above 70%†.

Case 2: Modest Uncertainty, Modest Postmarket Data Collection

Based on the relevant considerations, including the feasibility of postmarket data collection, FDA instead determines that a modest extent of uncertainty is appropriate, provided that there is a modest postmarket data collection in light of that uncertainty. For this case, assume that the underlying facts are such that the one-sided significance level could be 5%. With the same observed success rate of 74%, the sponsor would need only a sample size of **385** patients to be 95% confident that the success rate is above 70%†. If the sponsor chooses to conduct this study and the premarket evidence meets the performance goal, FDA would require a modest postmarket study as a condition of approval and flag the postmarket study on our website.

Case 3: High Uncertainty, Substantial Postmarket Data Collection

Suppose FDA instead determines that, based on the relevant considerations, including that the sponsor has a reliable and appropriate mechanism (e.g., registry, electronic health records) to complete timely postmarket data collection, an even higher extent of uncertainty is reasonable under the circumstances, provided that there is an even more substantial postmarket data

[48] *See* sections 513(a) and 515(d) of the FD&C Act (21 U.S.C. §§ 360c(a) and 360e(d)) and 21 CFR 860.7.

collection in light of that uncertainty. To illustrate how this might impact the premarket data collection, assume that the underlying facts are such that the one-sided significance level could be 20%. With the same observed success rate of 74%, the sponsor would only need a sample size of **125** patients to be 80% confident that the success rate is greater than 70%[†]. If the sponsor chooses to conduct this study and the premarket evidence meets the performance goal, FDA would require robust postmarket data collection as a condition of approval, using a registry or other appropriate means to help ensure the postmarket commitment is completed. If appropriate, FDA would also require, as a condition of approval, that the device labeling describe the postmarket data collection and its purpose. Also as appropriate, FDA would include such information in the SSED and flag postmarket studies that are a condition of approval for the device on our website.

Summary: One-sided significance levels and differences in sample size of premarket study

Scenario	One-sided significance level	Sample size†	Postmarket data collection and other measures in light of the greater uncertainty
Case 1: Conventional Uncertainty	2.5%	535	Not applicable
Case 2: Modest Uncertainty, Modest Postmarket Data Collection	5%	385	Modest postmarket data collection as a condition of approval Flag postmarket data collection on FDA's website
Case 3: High Uncertainty, Substantial Postmarket Data Collection	20%	125	Robust postmarket data collection using a registry (or other appropriate mechanism) as a condition of approval If appropriate, inclusion of information about the postmarket data collection and its purpose in labeling as a condition of approval and in the SSED Flag postmarket data collection on FDA's website

[†] Based on Clopper-Pearson binomial confidence interval. For illustration only, these calculations do not account for statistical power.

b. Breakthrough IVD Device

Consider a Breakthrough Device that is an in vitro diagnostic (IVD) laboratory test to be performed in central laboratories with patient specimens that require an invasive procedure for the diagnosis of a target condition. The test has two outputs (positive, negative) and the clinical performance of the binary qualitative test is described by a pair of clinical sensitivity and specificity, a pair of positive and negative likelihood ratios, and a pair of positive and negative predictive values for a particular prevalence of the target condition in the intended population. Suppose FDA considers the benefit-risk factors of the IVD test and the relevant non-clinical and/or clinical information, and determines that the clinical sensitivity should be ≥95% and clinical specificity should be ≥97%. The following two cases illustrate how there could be differences in sample sizes for the premarket clinical study where "conventional" uncertainty and greater uncertainty – that is reflected in the confidence level for the pair of sensitivity and specificity for the study – is appropriate under the circumstances, with implementation of appropriate postmarket controls, including postmarket data collection.

Case 1: Conventional Uncertainty

In this case, based on the considerations in Section IV and other relevant information, FDA determines that the confidence interval for the clinical performance of the IVD test should be 95% with a lower bound of the one-sided 97.5% confidence interval for the clinical sensitivity ≥89% and a lower bound of the one-sided 97.5% confidence interval for the clinical specificity ≥95%. As mentioned above, if the estimate of clinical sensitivity is 95%, a clinical study would be expected to include 120 subjects with the target condition for estimation of the clinical sensitivity because the two-sided 95% confidence interval for (114/120) is (89.5%; 97.7%). For a prevalence of 20% of the target condition in the intended use population, a premarket study would need 600 subjects (120 subjects with the target condition and 480 subjects without the target condition). This study size would also be acceptable for the estimation of clinical specificity because the two-sided 95% confidence interval for (466/480) is (95.1%; 98.3%).[49] So, the premarket study of 600 subjects provides information about the clinical performance of the IVD test, demonstrating clinical sensitivity of 95% and not less than 89% (with confidence 97.5%); clinical specificity of 97% and not less than 95% (with confidence 97.5%) and the overall confidence of 95% (=0.975·0.975) for the pair of clinical sensitivity and specificity.

Case 2: Greater Uncertainty for Breakthrough IVD Device, Modest Postmarket Data Collection

If, based on the considerations in Section IV and other relevant information (e.g., the new IVD laboratory test offers significant advantages over existing approved or cleared alternatives, such as, the new IVD test results can be obtained significantly faster for a condition with time-sensitive treatment and patient specimens used by the new test do not require any invasive procedures), FDA instead determines that greater uncertainty is appropriate, provided that there is a modest postmarket data collection in light of that uncertainty. For this case, assume that the underlying facts are such that the appropriate overall level of confidence could be 90% (level of

[49] Based on the score method binomial confidence intervals. The score method is advantageous in that it has better statistical properties (see reference Altman D.A., Machin D., Bryant T.N., Gardner M.J. Statistics with Confidence. 2nd ed. British Medical Journal, 2000 and CLSI EP12-A2 document). Score confidence bounds tend to yield narrower confidence intervals than Clopper-Pearson confidence intervals.

confidence for the lower bound of clinical sensitivity and specificity is 95%). If the estimate of clinical sensitivity is 95.0%, it is expected that a premarket study would include 80 subjects with the target condition for the estimation of clinical sensitivity because the two-sided 90% confidence interval for (76/80) would be (89.3%; 97.7%). For a condition with a prevalence of 20%, the premarket study would only need to include 400 subjects (80 subjects with the target condition and 320 subjects without the target condition). If the clinical specificity is 97%, the two-sided confidence interval for (311/320) would be (95.2%; 98.4%). Thus, a study with 400 subjects would provide information about the clinical performance of the IVD test with a clinical sensitivity of 95% and not less than 89% (with confidence of 95%); a clinical specificity of 97% and not less than 95% (with confidence of 95%) and an overall confidence of 90% (=0.95·0.95) for the pair of clinical sensitivity and specificity.

Summary: Confidence levels and differences in sample size of premarket study

Scenario	Confidence level for both sensitivity and specificity	Number of subjects with target condition present	Study size for prevalence=20%	Postmarket data collection in light of the greater uncertainty
Case 1: Conventional Uncertainty	95%	120	600	Not applicable
Case 2: Greater Uncertainty, Modest Postmarket Data Collection	90%	80	400	Modest postmarket data collection as a condition of approval Flag postmarket data collection on FDA's website

(2) Devices for Small Patient Populations – PMA

Consider a device intended to treat a disease that has an incidence of 10,000 new cases annually. The disease is relatively rare, but the patient population is not small enough for the device to qualify for an HDE. The device does not qualify for designation as a Breakthrough Device, because the disease is not life-threatening or irreversibly debilitating. However, the indicated disease is serious, and there are no alternative treatments available. Considering the lack of existing treatment options, the device's potential benefits to the patient population, the rarity of the disease, and other factors, as well as the relevant non-clinical and/or clinical information, as discussed in Case 2 and Case 3 below, a greater extent of uncertainty may be appropriate, provided that there is appropriate postmarket data collection in light of that uncertainty and other appropriate postmarket controls.

Suppose FDA considers the benefit-risk factors of the device for this indication and the relevant non-clinical and/or clinical information, and determines that a performance goal of 60% of the treated patients experiencing treatment success is acceptable. Assume the proposed premarket clinical study for this case is a single arm study. If the lower confidence limit of the success rate

estimate is greater than 60%, the endpoint would be met. The following three cases illustrate how there could be differences in sample sizes for the premarket clinical study where a "conventional," modest, and high extent of uncertainty – that is reflected in the one-sided significance level for the study – is appropriate under the circumstances, with implementation of appropriate postmarket controls, including postmarket data collection.

Case 1: Conventional Uncertainty

In this case, based on the considerations in Section IV and other relevant information, FDA determines that the one-sided significance level should be 2.5%. If the observed success rate is 66%, the sponsor would need a sample size of **274** patients to be 97.5% confident that the proportion of successful patients is greater than 60%[†].

Case 2: Modest Uncertainty, Modest Postmarket Data Collection

Based on the relevant considerations (e.g., where among other things, patient recruitment would be challenging and a conventional premarket study appears infeasible), FDA instead determines that a modest extent of uncertainty is appropriate, provided that there is a modest postmarket data collection in light of that uncertainty. For this case, assume that the underlying facts are such that the one-sided significance level could be 10%. With the same observed success rate of 66%, the sponsor would need only a sample size of **128** patients to be 90% confident that the success rate is above 60%[†]. If the sponsor chooses to conduct this study and the premarket evidence meets the performance goal, the FDA would require a relatively modest postmarket study as a condition of approval and flag the postmarket study on our website.

Case 3: High Uncertainty, Substantial Postmarket Data Collection

Suppose FDA instead determines that, based on the relevant considerations, including that the sponsor has a reliable and appropriate mechanism (e.g., registry, electronic health records) to complete timely postmarket data collection, an even higher extent of uncertainty is appropriate under the circumstances, provided that there is an even more substantial postmarket data collection in light of that uncertainty. To illustrate how this might impact the premarket clinical study, assume that the underlying facts are such that the one-sided significance level could be 20%. With the same observed success rate of 66%, the sponsor would only need a sample size of **65** patients to be 80% confident that the success rate is above 60%[†]. If the sponsor chooses to conduct this study and the premarket evidence meets the performance goal, FDA would require, as a condition of approval, a relatively robust postmarket data collection, using a registry or other appropriate means to help ensure the postmarket commitment is completed. If appropriate, FDA would also require, as a condition of approval, that the device labeling describe the postmarket data collection and its purpose. Also as appropriate, FDA would include such information in the SSED and flag postmarket studies that are a condition of approval for the device on our website.

Summary: One-sided significance levels and differences in sample size of premarket study

Scenario	One-sided significance level	Sample size[†]	Postmarket data collection and other measures in light of the greater uncertainty
Case 1: Conventional Uncertainty	2.5%	274	Not applicable
Case 2: Modest Uncertainty, Modest Postmarket Data Collection	10%	128	Modest postmarket data collection as a condition of approval Flag postmarket data collection on FDA's website
Case 3: High Uncertainty, Substantial Postmarket Data Collection	20%	65	Robust postmarket data collection using a registry (or other appropriate mechanism) as a condition of approval If appropriate, inclusion of information about the postmarket data collection and its purpose in labeling as a condition of approval and in the SSED Flag postmarket data collection on FDA's website

[†] Based on Clopper-Pearson binomial confidence interval. For illustration only, these calculations do not account for statistical power.