Section 3308 of The Food and Drug Omnibus Reform Act of 2022 (FDORA) enacted as part of the Consolidated Appropriations Act, 2023 (December 29, 2022) amended section 517A(a)(1) of the Federal Food, Drug, and Cosmetic Act. As amended, section 517A(a)(1) no longer includes Breakthrough Device Designation Requests. For more information, please contact the CDRH Ombudsman at CDRHOmbudsman@fda.hhs.gov.

Contains Nonbinding Recommendations

Breakthrough Devices Program

Guidance for Industry and Food and Drug Administration Staff

Document issued on September 15, 2023.

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This document supersedes "Breakthrough Devices Program," issued on December 18, 2018.

For questions about this document regarding CDRH-regulated devices, contact the Office of Clinical Evidence and Analysis (OCEA) at 301-796-5550 or BreakthroughDevicesProgram@fda.hhs.gov. For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach, and Development (OCOD) at 1-800-835-4709 or 240-402-8010, or by email at ocod@fda.hhs.gov.

U.S. FOOD & DRUG ADMINISTRATION

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research

Preface

Public Comment

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Breakthrough Devices Program

Guidance for Industry and Food and Drug Administration Staff

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff or Office responsible for this guidance as listed on the title page.

I. Introduction[1]

This guidance document describes policies that FDA intends to use to implement section 515B of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 360e-3), as created by section 3051 of the 21st Century Cures Act (Cures Act),[2] amended by section 901 of the FDA Reauthorization Act of 2017,[3] and amended by section 3001 of the SUPPORT for Patients and Communities Act[4] (the SUPPORT Act) (the "Breakthrough Devices Program"). The Breakthrough Devices Program is a voluntary program for certain medical devices and device-led combination products[5] that provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions. It is available for devices and device-led combination products which are subject to review under a premarket approval application (PMA), premarket notification (510(k)), or De Novo classification request ("De Novo request").[6] The Breakthrough Devices Program may also be applicable to certain devices that benefit populations impacted by health and/or health care disparities, thereby promoting and advancing health equity. In addition, consistent with our obligations under the SUPPORT Act,[7] the Breakthrough Devices Program may be available for certain non-addictive medical products to

[1] The Office of Combination Products (OCP) and the Center for Drug Evaluation and Research (CDER) were consulted in the preparation of this guidance.
[2] Public Law 114-255.
[3] Public Law 115-52.
[4] Public Law 115-271.
[5] A combination product is defined in 21 CFR 3.2. For purposes of this guidance, device-led combination products refer to combination products subject to review under a premarket approval application (PMA), premarket notification (510(k)), or De Novo classification request.
[6] Breakthrough Device designation may be requested at any time prior to the submission of a PMA, 510(k), or De Novo request. Sponsors should only request Breakthrough Device designation if they intend to pursue one of these marketing pathways. Other marketing pathways, such as the Humanitarian Device Exemption (HDE) Program, are not eligible for consideration under the Breakthrough Devices Program. For additional considerations for devices eligible for the HDE Program, please refer to FDA's guidance, available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/humanitarian-device-exemption-hde-program. For additional considerations regarding Humanitarian Use Device (HUD) Designations, please refer to FDA's guidance, available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/humanitarian-use-device-hud-designations.
[7] Public Law 115-271.

treat pain or addiction (FD&C Act section 515B (21 U.S.C. 360e-3)).[8] The Breakthrough Devices Program is intended to help patients have more timely access to designated medical devices by expediting their development, assessment, and review, while preserving the statutory standards for premarket approval, 510(k) clearance, and De Novo marketing authorization, consistent with the Agency's mission[9] to protect and promote public health.

The Breakthrough Devices Program supersedes the Expedited Access Pathway (EAP), which was launched in 2015. The Breakthrough Devices Program contains features of the EAP as well as the Innovation Pathway (first piloted in 2011; the pilot is now discontinued), both of which were intended to facilitate the development and expedite the review of breakthrough technologies. Due to consistency in vision and designation criteria between the precursor EAP Program and the Breakthrough Devices Program, FDA now considers devices granted designation under the EAP to be part of the Breakthrough Devices Program.

The Breakthrough Devices Program also supersedes the Priority Review Program, which implemented statutory criteria for granting priority review to premarket submissions for medical devices[10] and included standard procedures to achieve an efficient priority review process. However, consistent with Section 515B of the FD&C Act, devices designated as Breakthrough Devices will receive prioritized review (Section II.F).

FDA provides information about this program on the Breakthrough Devices Program Webpage.[11]

For the current edition of the FDA-recognized standard(s) referenced in this document, see the FDA Recognized Consensus Standards Database.[12] If submitting a Declaration of Conformity to a recognized standard, we recommend you include the appropriate supporting documentation. For more information regarding use of consensus standards in regulatory submissions, please refer to the FDA guidance titled "Appropriate Use of Voluntary Consensus Standards in Premarket Submissions for Medical Devices"[13] and "Standards Development and the Use of Standards in Regulatory Submissions Reviewed in the Center for Biologics Evaluation and Research."[14]

In general, FDA's guidance documents 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 guidances means that something is suggested or recommended, but not required.

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[8] The considerations set forth in this guidance document apply to FDA's review of devices as non-addictive methods to treat pain or addiction.

[9] Statement of FDA Mission can be found at https://www.fda.gov/AboutFDA/WhatWeDo/.

[10] FDA's guidance, "Priority Review of Premarket Submissions for Devices," issued on May 17, 2013, implemented former section 515(d)(5) of the FD&C Act (as in effect prior to the date of enactment of the Cures Act), which applied only to PMAs. Because of the potential public health importance of devices warranting priority review status, FDA also applied the priority review criteria to other types of premarket submissions for devices. FDA withdrew this guidance on August 3, 2017. See https://www.fda.gov/medical-devices/guidance-documents-medical-devices-and-radiation-emitting-products/withdrawn-guidance.

[11] Available at https://www.fda.gov/medical-devices/how-study-and-market-your-device/breakthrough-devices-program.

[12] Available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm.

[13] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/appropriate-use-voluntary-consensus-standards-premarket-submissions-medical-devices.

[14] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/standards-development-and-use-standards-regulatory-submissions-reviewed-center-biologics-evaluation.

II. Program Principles

The Breakthrough Devices Program is comprised of two phases. The first is the Designation Request phase, in which an interested sponsor of a device requests that FDA grant that device Breakthrough Device designation (Section III). The second phase encompasses actions to expedite development of the device and the prioritized review of subsequent regulatory submissions (e.g., Pre-Submissions, marketing submissions) (Section IV).

The principles below describe the philosophy of the Breakthrough Devices Program and, in general, the approach FDA intends to take in an effort to help expedite the development and review of devices designated as Breakthrough Devices under section 515B(d)(1) of the FD&C Act (21 U.S.C. 360e-3(d)(1)). FDA intends to evaluate resource allocation in collaboration with the sponsor throughout the development process to make the best use of FDA's resources and maximize the impact of the Breakthrough Devices Program. Devices designated as Breakthrough Devices, which subsequently receive marketing authorization, have no additional limitations solely by virtue of their designation.

A. Interactive and Timely Communication

For Breakthrough Devices, FDA intends to provide interactive and timely communication with the sponsor during device development and throughout the review process[15] for Q-Submissions,[16] Investigational Device Exemptions (IDEs), 510(k)s, De Novo requests, PMAs, and/or certain PMA supplements (i.e., Panel Track Supplements, 180 Day PMA Supplements) for which the subject device was designated as a Breakthrough Device. This applies to devices as well as to device-led combination products.

To best facilitate collaborative dialogue, the following, where applicable, are recommended for communications between FDA and the sponsor:

- discussion and agreement between FDA and the sponsor regarding goals of interactions and feasibility of response timelines;
- use of "track changes" and redlined versions of any document being revised interactively to efficiently and transparently communicate any updates; and
- use of summary tables to document points of agreement and previous interactions.

FDA also intends to assign staff to be available within a reasonable time to address questions by institutional review committees concerning the conditions and clinical testing expectations applicable to the investigational use of a Breakthrough Device.[17]

Given that there may be novel scientific aspects of products in the Breakthrough Devices Program, FDA may need to interact with external experts or an Advisory Committee to reach various regulatory

[15] See section 515B(e)(1)(D) of the FD&C Act (21 U.S.C. 360e-3(e)(1)(D)).
[16] For information on Q-Submissions, please refer to the FDA guidance, "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program," at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program.
[17] See section 515B(e)(1)(H) of the FD&C Act (21 U.S.C. 360e-3(e)(1)(H)).

decisions.[18] In the event that such consultation is undertaken, FDA will disclose to the sponsor, no less than five business days in advance, the topics for discussion. FDA will also provide the sponsor with the opportunity to recommend external experts.[19] After any consultation with external experts outside of an Advisory Committee meeting, FDA intends to provide the sponsor with a list of any topics discussed with external experts that differ from the topics identified to the sponsor in communications prior to the consultation and an explanation of any decisions on the Breakthrough Device based in part on the consultation. When FDA refers a matter regarding a Breakthrough Device to a Medical Devices Advisory Committee panel, CDRH intends to follow the procedures described in its guidance document entitled "Procedures for Meetings of the Medical Devices Advisory Committee."[20] CBER intends to hold either a Blood Products Advisory Committee (BPAC) or Cellular, Tissue and Gene Therapies Advisory Committee (CTGTAC) meeting when seeking Advisory Committee input on a Breakthrough Device.

B. Pre/Postmarket Balance of Data Collection

As with all devices subject to a PMA, Breakthrough Devices subject to a PMA must still meet the statutory standard of reasonable assurance of safety and effectiveness at the time of approval. For PMAs designated as Breakthrough Devices, FDA intends to use timely postmarket data collection, when scientifically appropriate, to facilitate expedited and efficient development and review of the device.[21] In accordance with the FDA guidance, "Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications,"[22] as part of FDA's benefit-risk determination for Breakthrough Devices subject to a PMA, FDA may consider the amount and nature of data that may be collected in the postmarket setting, rather than premarket, and the extent of uncertainty that may be appropriate in the benefit-risk profile at the time of approval.[23] In all FDA premarket approval decisions, there is some extent of uncertainty about the benefits and risks of the device. We may not have definitive answers to all questions relating to the benefits and risks of the device at the time of approval because the time and cost of such data collection would adversely affect public health by significantly delaying the availability of medical devices that may improve the health of patients (e.g., to do so for a particular device may require clinical studies that enroll thousands of subjects to more fully assess all risks, such as rare adverse events). The extent of uncertainty that may be appropriate at the time of approval depends on, among other factors, the probable benefits of the device, and the relevant non-clinical and clinical information about the device.

FDA will only approve a PMA if it determines that there is reasonable assurance of safety and effectiveness. As part of the benefit-risk determination for Breakthrough Devices subject to a PMA, FDA may accept a greater extent of uncertainty of the benefit-risk profile for these devices if appropriate under the circumstances, including that the uncertainty is sufficiently balanced by other factors, such as the probable benefits for patients to have earlier access to the device (e.g., a device that treats a life-

[18] Under section 515B(e)(1)(G) of the FD&C Act (21 U.S.C. 360e-3(e)(1)(G)), FDA must provide for advisory committee input, as it determines appropriate for PMAs (including in response to the sponsor's request).
[19] See section 515B(e)(1)(F) of the FD&C Act (21 U.S.C. 360e-3(e)(1)(F)).
[20] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/procedures-meetings-medical-devices-advisory-committee.
[21] See section 515B(e)(2)(C) of the FD&C Act (21 U.S.C. 360e-3(e)(2)(C)).
[22] 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.
[23] Section 515(c)(5)(C) of the FD&C Act (21 U.S.C. 360e(c)(5)(C)) 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. See section 515B(e)(2)(B) of the FD&C Act (21 U.S.C. 360e- 3(e)(2)(B)).

threatening disease when no alternative treatments are available) and adequate postmarket controls to support premarket approval. Generally, weighing the benefits against the risks for Breakthrough Devices for which we would accept a greater extent of uncertainty adds another dimension to the benefit-risk calculus. Specifically, as part of FDA's benefit-risk determination, FDA intends to weigh the device's impact on patient health, including the probable benefit of earlier access to the device, against the probable risk of harm to patients from the device should subsequent data collection demonstrate that the device is ineffective or unsafe. FDA's guidance, "Balancing Premarket and Postmarket Data Collection for Devices Subject to Premarket Approval"[24] provides more information regarding FDA's current policy on balancing premarket and postmarket data collection during FDA's review of PMAs.

C. Efficient and Flexible Clinical Study Design

FDA intends to "take steps to ensure that the design of clinical trials is as efficient and flexible as practicable, when scientifically appropriate."[25] This may include consideration of the following (note that the examples listed below are not intended to be an exhaustive list):

- prespecified endpoints[26] regarding the minimum clinically meaningful effect;
- intermediate and surrogate endpoints where evidence is provided to support the endpoint as reasonably likely to predict the clinical benefit of a device;
- composite endpoints with an explicit rationale for the meaningful effect size; and
- adaptive study designs.

D. Review Team Support

For each Breakthrough Device submission received, FDA will route the submission to the appropriate organizational unit. An FDA manager in that unit will assess the submission and assign the most appropriate individual to lead the review team based upon training, expertise, experience, and the ability to quickly and interactively resolve complex issues. The review team lead is responsible for coordinating the scientific and regulatory review including developing documentation to support a recommendation to management and interacting with the sponsor. The review team lead, in conjunction with management, will determine the need for and assign additional staff with subject matter expertise to review specific aspects of the submission; for example, by providing consultation on the disease or condition at issue or on a clinical study design. Staff reviewing Breakthrough Devices will be experienced with innovative approaches to regulatory science and clearly communicating FDA's expectations during the device development process.

Breakthrough Device review teams will undergo periodic training to ensure consistent and efficient application of the principles and features outlined in this guidance document as well as to communicate productive examples across projects. This training may include team meetings, sponsor engagement, patient interactions, and participation at scientific and regulatory meetings to help ensure teams are up to date in the technological advancements of their respective areas of scientific and device expertise and

[24] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/balancing-premarket-and-postmarket-data-collection-devices-subject-premarket-approval.
[25] See section 515B(e)(2)(B) of the FD&C Act (21 U.S.C. 360e-3(e)(2)(B)).
[26] In clinical studies for in vitro diagnostics, the endpoint may be analytically, clinically, or both analytically and clinically acceptable performance when compared to a comparator method with the same intended use.

prepared to apply novel approaches to regulatory and device development challenges.

E. Senior Management Engagement

Senior management (e.g., Office director or designee representing Office director) will be involved in the review process for Breakthrough Device submissions to ensure consistent application of Program principles and facilitate the review process. They will work with Breakthrough Device review teams to facilitate the sponsor's efficient development of the device and FDA's efficient review of related submissions. To support efficient and timely dispute resolution, senior management will be engaged in projects when points of disagreement that cannot be quickly resolved are identified by the FDA review team or the sponsor during the device development or review process.

F. Priority Review

All submissions for devices designated as Breakthrough Devices will receive priority review, meaning that the review of the submission is placed at the top of the appropriate review queue and receives additional review resources, as needed. Although priority review for devices is intended to help expedite patient access to certain devices important to public health, FDA's past experience with the Priority Review Program indicates that review times for marketing submissions may take longer for Breakthrough Devices than for other devices because of the novel scientific issues these devices may raise. The review times for marketing submissions of device-led combination products may also take longer because such products may raise unique scientific and regulatory issues. We believe that the Breakthrough Devices Program may enable patients to have more timely access to these devices than they would otherwise because of the earlier interaction between FDA and sponsors during the device development process.

In order to benefit from priority review status under the Breakthrough Devices Program, the commitment on behalf of the sponsor to resolve all scientific and regulatory issues should match that of FDA. It will only be through effective communication (e.g., interactive review), collaboration, and a commitment to fulfilling all regulatory and scientific requirements that FDA and the sponsor can speed the availability of safe and effective products.

G. Manufacturing Considerations for PMA Submissions

A device must be in conformance with the Quality System regulation ("QS Reg"; 21 CFR part 820),[27] and the sponsor must submit adequate information in a PMA to meet the requirements under section 515(c)(1)(C) of the FD&C Act (21 U.S.C. 360e(c)(1)(C)) and 21 CFR 814.20(b)(4)(v). As with other PMAs, sponsors of a Breakthrough Device should submit PMA information as described in the FDA

[27] On February 23, 2022, FDA proposed to amend the device QS regulation, 21 CFR part 820, to align more closely with international consensus standard for the Quality Management System of devices (87 FR 10119; available at https://www.federalregister.gov/documents/2022/02/23/2022-03227/medical-devices-quality-system-regulation-amendments). Specifically, FDA proposed to withdraw the majority of the current requirements in part 820 and instead incorporate by reference the 2016 edition of the International Organization for Standardization (ISO) 13485, Medical devices - Quality management systems for regulatory purposes, in part 820. As stated in that proposed rule, the requirements in ISO 13485 are, when taken in totality, substantially similar to the requirements of the current part 820, providing a similar level of assurance in a firm's quality management system and ability to consistently manufacture devices that are safe and effective and otherwise in compliance with the FD&C Act. FDA intends to finalize this proposed rule expeditiously. When the final rule takes effect, FDA will also update the references to provisions in 21 CFR part 820 in this guidance to be consistent with that rule.

guidance, "Quality System Information for Certain Premarket Application Reviews."[28]

Section 515B(e)(1)(E) of the FD&C Act (21 U.S.C. 360e-3(e)(1)(E)), directs FDA to expedite its review of manufacturing and quality systems compliance, as applicable, for purposes of expediting the development and review of Breakthrough Devices. For submission types that typically require a preapproval inspection (i.e., PMA), FDA intends to expedite the review of manufacturing and quality systems compliance for devices in the Breakthrough Devices Program. FDA may accept less quality system and manufacturing information in a PMA if the sponsor satisfies the statutory and regulatory requirements using an alternative approach to submitting all of the items listed in the FDA guidance, "Quality System Information for Certain Premarket Application Reviews." For example, this may occur when the sponsor has a good track record for quality systems compliance and there are no new manufacturing issues that could adversely impact product quality or performance.

In appropriate cases, FDA may decide not to conduct an inspection of certain manufacturing sites prior to approval of a Breakthrough Device. In general, FDA would review the sponsor's quality system and manufacturing information and make a decision about inspecting finished device manufacturing sites as follows:

- For finished device manufacturing sites with no prior inspectional history or no inspectional history within the five-year period prior to the filing date of the application, FDA would generally inspect those sites before approval of the Breakthrough Device.

- For finished device manufacturing sites that have been inspected within the two-year period prior to the filing date of the PMA, for which the inspectional outcome was 'No Action Indicated' or 'Voluntary Action Indicated' and for which the inspectional coverage is relevant to the PMA at issue, FDA may determine that it is appropriate to inspect those sites after approval of the Breakthrough Device.

- For finished device manufacturing sites that have been inspected within a period of two to five years prior to the filing date of the PMA, for which the inspectional outcome was 'No Action Indicated' or 'Voluntary Action Indicated' and for which the inspectional coverage is relevant to the PMA at issue, FDA may determine that it is appropriate to inspect those sites after the Breakthrough Device is approved in situations where, in addition to submitting all other information required in a PMA under section 515(c)(1) of the FD&C Act (21 U.S.C. 360e(c)(1)) and 21 CFR 814.20, the sponsor submits the following:

    - a declaration stating that all activities at the site comply with the QS Reg (21 CFR part 820); and

    - information, initially developed as part of design validation (21 CFR 820.30(g)) and current as of the filing date of the PMA, demonstrating that the sponsor's risk analysis activities included evaluation of risk associated with the design, manufacturing, and use of the device, and that risk has been reduced to acceptable levels. The sponsor could do this, for example, using standards such as the currently FDA-recognized version of ISO 14971: *Medical devices – Application of risk management to medical devices*.

[28] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/quality-system-information-certain-premarket-application-reviews.

Where an inspection is not conducted prior to approval of the PMA for a Breakthrough Device, FDA intends to conduct an inspection within 12 months after approval. In appropriate circumstances, FDA may consider such a post approval inspection that is classified as 'Official Action Indicated' and for which deviations are not brought into QS Reg conformance within a reasonable time after receipt of written notice to be grounds for PMA withdrawal under section 515(e)(1)(E) of the FD&C Act (21 U.S.C. 360e(e)(1)(E)).

It is important to note that there may be additional challenges to fully implementing this policy for device-led combination products designated as Breakthrough because these products are subject to different manufacturing requirements due to the presence of both device and drug or biologic constituents.[29]

For clarification, when a PMA sponsor's manufacturing sites are not ready for inspection, or have been inspected and classified as 'Official Action Indicated,' the sponsor may receive an approvable PMA letter pending a QS Reg decision from FDA. It should be noted that this applies to PMA sponsors that are manufacturing their own device as well as to sponsors who intend to have another entity manufacture their device for commercial distribution in the U.S. FDA generally would then approve the device once there is adequate assurance of compliance regarding the applicable quality systems of the manufacturer(s).

III. Designation Request

A Breakthrough Device designation request is the mechanism by which sponsors request entry into the Breakthrough Devices Program and FDA renders and communicates a decision on the request. When submitting a request for Breakthrough Device designation, sponsors should clearly indicate the proposed indications for use for which they are seeking designation, as illustrated in Appendix 1. The proposed indication(s) may target a subset of a broader disease population.

A. Designation Criteria

The designation criteria, as defined in section 515B(b) of the FD&C Act (21 U.S.C. 360e-3(b)), provide for a Program for devices:

> "(1) that provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating human disease or conditions; and
>
> (2)(A) that represent breakthrough technologies;
>
> (B) for which no approved or cleared alternatives exist;
>
> (C) that offer significant advantages over existing approved or cleared alternatives, including the potential, compared to existing approved alternatives, to reduce or eliminate the need for hospitalization, improve patient quality of life, facilitate patients' ability to manage their own care (such as through self-directed personal assistance), or establish long-term clinical efficiencies; or
>
> (D) the availability of which is in the best interest of patients."

[29] See 21 CFR Part 4, Subpart A; see also final rule for Current Good Manufacturing Practice Requirements for Combination Products, published in Federal Register of January 22, 2013 (78 FR 4307).

Therefore, devices must meet the first criterion (section 515B(b)(1) of the FD&C Act) and at least one of the sub-paragraphs listed for the second criterion (section 515B(b)(2) of the FD&C Act) in order to be granted Breakthrough Device designation.

In addition, section 515B(c) of the FD&C Act (21 U.S.C. 360e-3(c)) states:

> "Any such request for designation may be made at any time prior to the submission of an application under section 515(c) [21 U.S.C 360e(c)], a notification under section 510(k) [21 U.S.C. 360(k)], or a petition for classification under section 513(f)(2) [21 U.S.C. 360c(f)(2)]."

B. Designation Considerations

(1) First Criterion

In determining whether a device meets the criterion of providing "for more effective treatment or diagnosis of life-threatening or irreversibly debilitating human disease or condition,"[30] FDA considers the following three factors:

a. Whether a Device Provides for "More Effective" Treatment or Diagnosis

Because decisions on requests for designation will be made prior to marketing authorization of a device, for the purposes of designation, FDA believes it is appropriate to consider whether there is a reasonable expectation that a device could provide for more effective treatment or diagnosis relative to the current standard of care (SOC) in the U.S. A complete set of clinical data is not required for designation. Instead, a sponsor should demonstrate a reasonable expectation that the device could provide for more effective treatment or diagnosis of the disease or condition identified in the proposed indications for use. This includes a reasonable expectation that the device could function as intended (technical success) and that a functioning device could more effectively treat or diagnose the identified disease or condition (clinical success). Mechanisms for demonstrating a reasonable expectation of technical and clinical success could include literature or preliminary data (bench, animal, or clinical). For example, a sponsor might provide preliminary bench data to support the potential for technical success and literature to support that a given principle of operation could more effectively treat or diagnose the identified disease or condition.

The level and type of evidence needed to determine whether a device is reasonably expected to "provide for more effective treatment or diagnosis" may vary depending on the intended use of the device, its technology and features, and the available standard of care alternatives. When evaluating this part of the first criterion, FDA considers the totality of information regarding the proposed device, its function, potential for technical success, potential for clinical success, potential for a clinically meaningful impact, and its potential benefits and risks. The determination of whether a device is reasonably expected to "provide for more effective treatment or diagnosis" is based upon all these factors.[31]

[30] See section 515B(b)(1) of the FD&C Act (21 U.S.C. 360e-3(b)(1)).

[31] The considerations set forth for whether a device is reasonably expected to "provide for more effective treatment or diagnosis" are limited to evaluating the first Breakthrough criterion within the scope of this guidance.

b. Whether a Disease or Condition is "Life -Threatening"

FDA considers a disease or condition life-threatening for purposes of the Breakthrough Devices Program if it is a disease or condition for which the likelihood of death is high unless the course of the disease is interrupted in a population or subpopulation. Examples of life-threatening diseases or conditions include, but are not limited to, acute stroke, myocardial infarction, cancer, and trauma.

c. Whether a Disease or Condition is "Irreversibly Debilitating"

For purposes of the Breakthrough Devices Program, FDA considers a disease or condition associated with morbidity that has substantial impact on day-to-day functioning to be irreversibly debilitating for a population or subpopulation. Short-lived and self-limiting morbidity will usually not be sufficient. Irreversible disease or conditions may, in certain cases, include diseases or conditions that are persistent or recurrent. Whether a disease or condition is "irreversibly debilitating" is based on its impact on such factors as survival, day-to-day functioning, and the likelihood that the disease or condition, if left untreated, will progress to a more serious disease or condition. Examples include cancer, amyotrophic lateral sclerosis (ALS), stroke, and large ST segment elevation myocardial infarction (STEMI; while patients with STEMI and stroke can improve with medication and rehabilitation, the effects are not reversible and can be debilitating).

(2) Second Criterion

As noted above, to qualify for Breakthrough Device designation, in addition to meeting the first criterion, a sponsor must also demonstrate that its device meets one of the four sub-paragraphs under the second criterion.

a. Device Represents Breakthrough Technology

When determining whether a device represents a "breakthrough technolog[y],"[32] FDA considers whether the device represents a novel technology or novel application of an existing technology that has the potential to lead to a clinical improvement in the diagnosis, treatment (including monitoring of treatment), cure, mitigation, or prevention of the life-threatening or irreversibly debilitating disease or condition. Illustrative examples of technologies that would have been considered breakthrough at the time they came to market include:

- A transcatheter heart valve that is delivered transcutaneously and does not require open heart surgery, thereby decreasing the risks of the procedure. This breakthrough technology has the potential to provide a clinically meaningful advantage in a patient population with few options.

- An internal hemostatic device for the temporary control of bleeding from junctional wounds and non-compressible wounds, which are not amenable to tourniquet application in the battlefield. This device offers immediate care for severe bleeding wounds in a battlefield setting until surgical care is available, offering patients a potentially life-saving treatment when other methods of stopping severe bleeds are not an option.

- A gene signature test that provides prognostic information for a cancer patient such that the information helps clinicians personalize the benefit-risk profile of a variety of

[32] See section 515B(b)(2)(A) of the FD&C Act (21 U.S.C. 360e-3(b)(2)(A)).

therapeutic options and treatment strategies.

- A genetic test capable of identifying DNA mutations using blood from cancer patients may offer patients a more convenient, non-invasive sampling method compared to surgery, which has the potential for serious risks.

b. No Approved or Cleared Alternatives Exist

When determining whether the device meets the criterion that "no approved or cleared alternatives exist,"[33] FDA considers whether there is a drug, biological product, device, or combination product that has received FDA marketing authorization after premarket review for the same indication(s) being considered (i.e., whether there is an alternative product that FDA has approved, cleared, or licensed, or for which FDA has granted a De Novo request).

In addition to being an "approved or cleared" alternative, a product should be consistent with the U.S. SOC. There may be a substantial number of currently approved or cleared medical products with varying relevance in the diagnosis and treatment of a life-threatening or irreversibly debilitating disease in the U.S., including devices that are no longer used or are used only rarely. FDA's determination as to whether there is an approved or cleared alternative generally focuses only on options that reflect the current SOC for the specific indication (including the disease stage) for which the product is being developed.

In evaluating the current SOC, FDA considers recommendations by authoritative scientific bodies based on clinical evidence and other reliable information, including such information submitted by the sponsor, that reflects current clinical practice. In the absence of a well- established and documented SOC, FDA may consult with special government employees (SGEs) or other experts for advice in assessing whether an approved or cleared medical product is relevant to the current SOC. When a proposed indication for the new device targets a subset of a broader disease population, the SOC for the broader population, if there is one, generally is considered available therapy for the subset. Over the course of new device development, it is foreseeable that the SOC for a given condition may evolve (e.g., because of the approval of a new device or new information about alternative treatments). For the purpose of determinations on Breakthrough Device designation requests, FDA intends to determine what constitutes an "alternative" at the time of the request for Breakthrough Device designation.

Examples of devices for which no approved or cleared alternative exists at the time designation is requested include:

- An ablation catheter that offers the potential ability to treat atrial fibrillation. Catheters were approved for treatment of atrial flutter, and there was no legally marketed ablation catheter indicated for the treatment of atrial fibrillation. Therefore, at the time of review, the ablation catheter met the criteria for "no approved or cleared alternative."

- A first-of-a-kind testing device to aid in the diagnosis of Parkinson's Disease. While devices exist to monitor tremors that may be associated with Parkinson's Disease, no device intended to aid in the diagnosis of Parkinson's Disease has received FDA marketing authorization. A device that could differentiate between Parkinsonian and non-Parkinsonian Disease tremor would be considered first-of-a-kind and meet the criterion for having "no approved or cleared alternatives."

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

c. Device Offers Significant Advantages over Existing Approved or Cleared Alternatives

In determining whether a device meets the criterion of offering "significant advantages over existing approved or cleared alternatives,"[34] FDA considers the potential, compared to existing approved or cleared alternatives, "to reduce or eliminate the need for hospitalization, improve patient quality of life, facilitate patients' ability to manage their own care (such as through self- directed personal assistance), or establish long-term clinical efficiencies."[35]

Examples of devices that have the potential to offer significant advantages over existing approved or cleared alternatives include:

- a diagnostic product intended to improve diagnosis or detection of a life-threatening or irreversibly debilitating disease or condition in a way that would lead to improved outcomes (e.g., an in vitro diagnostic product (IVD) for earlier diagnosis of preeclampsia);

- a product intended to improve or prevent a serious treatment-related side effect associated with an available product for treating a life-threatening or irreversibly debilitating disease or condition;

- a product intended to treat a life-threatening or irreversibly debilitating disease or condition that does not have a serious adverse effect associated with an available product for treating this disease/condition; and

- a product intended to treat or diagnose a life-threatening or irreversible disease or condition that results in more efficient or safer clinical operation.

d. Device Availability is in the Best Interest of Patients

In determining whether the device meets the criterion "availability [of the device] is in the best interest of patients,"[36] FDA considers whether the proposed device and indications for use provide another type of specific public health benefit.

An example of a device, the availability of which is in the best interest of patients, could be a group of molecular tests to identify a large number of potential pathogens simultaneously, including common, rare, and/or emerging pathogens. More rapid access to more detailed diagnostic information can better guide optimal patient care and may yield better patient outcomes. However, these devices also suffer major challenges not only in comparing against reference methods but also in obtaining the appropriate sample base to reliably verify the more rare pathogens in the panel. This can result in the target panel of these tests being reduced in order to generate data to support FDA marketing authorization. The Breakthrough Devices Program may facilitate the developers' ability to test new wide-scope IVDs for both common and rare pathogens, resulting in devices with a broader diagnostic scope being brought to

[34] See section 515B(b)(2)(C) of the FD&C Act (21 U.S.C. 360e-3(b)(2)(C)). As noted above in Section III.B(2)b of this guidance, for purposes of the Breakthrough Devices Program, we consider an "approved or cleared alternative" to be a product that FDA has approved, cleared, licensed, or for which FDA has granted a De Novo request for the same indication(s) as that being considered in the breakthrough designation request.
[35] See section 515B(b)(2)(C) of the FD&C Act (21 U.S.C. 360e-3(b)(2)(C)).
[36] See section 515B(b)(2)(D) of the FD&C Act (21 U.S.C. 360e-3(b)(2)(D)).

market. Also, this program could facilitate more rapid marketing authorization of modifications to these tests as new and emerging pathogens are discovered or proposed for addition to the panels.

In addition, the criterion of being in the best interest of patients may apply when the device has a benefit for patients who are unable to tolerate available therapy, whose disease has failed to respond to available therapy, or for whom the treatment can be used effectively with other critical agents that cannot be combined with available therapy. This criterion may also apply if the device:

- avoids serious harm that can occur with available therapy;
- avoids serious harm that causes discontinuation of treatment of a life-threatening or irreversibly debilitating disease or condition; or
- reduces the potential for harmful interactions with other therapies.

In addition, this criterion may apply to a device that was designed or modified to address an unanticipated serious failure occurring in a critical component of an approved or cleared device for which there are no alternatives or for which alternative treatment would entail substantial risk of morbidity for the patient. A device may also satisfy this criterion if it provides an additional benefit, such as improved patient compliance that is expected to lead to a reduction in serious adverse outcomes. Furthermore, this criterion may apply if the device addresses an emerging or anticipated public health need, such as a device shortage or public health emergency.

A product developed by a sponsor who is working with a Federal agency on the development of medical devices to address a national security issue may be considered to meet this criterion. To support a request for designation under this criterion, it may be helpful to include a letter in the designation request from the Federal agency (e.g., Department of Defense, Department of Homeland Security) identifying the specific device or device type and indicating that its commercial availability is of particular importance to our national security.

Examples of devices for which availability would have been considered in the best interest of patients at the time they came to the market are as follows:

- an insulin pump that features a new mechanism to detect and respond to low blood glucose; and
- an IVD assay that detects a genomic variant for the purposes of identifying patients with certain cancers who are eligible for treatment with a specific drug. In some situations, for those patients who do not possess the variant, a therapeutic product may have severe toxicities and be detrimental without providing benefit to the patient. For this reason, use of the assay is necessary for safe and effective use of the drug and is therefore in the best interest of patients. For more information on in vitro companion diagnostic devices, please refer to the FDA guidance, "In Vitro Companion Diagnostic Devices."[37]

Finally, FDA may consider relevant patient experiences and perspectives when evaluating whether a device meets the designation criterion of availability being in the best interests of patients. FDA may also consider relevant patient experiences and perspectives when evaluating other designation criteria for purposes of a Breakthrough Device designation request. This may include information on the relative

[37] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/in-vitro-companion-diagnostic-devices.

value of the perceived benefits and risks of a specific device to treat or diagnose a life threatening or irreversibly debilitating disease or condition. Sponsors interested in presenting patient preference information in support of their Breakthrough Device designation request may refer to the FDA guidances "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"[38] and "Principles for Selecting, Developing, Modifying, and Adapting Patient-Reported Outcome Instruments for Use in Medical Device Evaluation"[39] for additional information.

(3) Additional Considerations

a. Regulatory Path

Section 515B of the FD&C Act states that Breakthrough Device designation may be requested "any time prior to the submission of an application under section 515(c) [21 U.S.C 360e(c)], a notification under section 510(k) [21 U.S.C. 360(k)], or a petition for classification under section 513(f)(2) [21 U.S.C. 360c(f)(2)]."[40]

Therefore, as part of the designation request review, FDA considers whether the expected marketing application for the device is a PMA, 510(k), or De Novo request. Sponsors should indicate which marketing application type (PMA, 510(k), or De Novo request) they intend to submit and include a rationale for this approach in support of their Breakthrough Device designation request. FDA's designation decision does not constitute a formal decision regarding the applicable regulatory pathway or device classification, but does indicate that, based on the information provided in the designation request and other information known at the time, the Agency expects that submission of a PMA, 510(k), or De Novo request will be necessary for marketing authorization. FDA does not intend to specify in its decision on the designation request which type of marketing application the sponsor will need to submit for the subject device.

Consistent with section 515B(c) of the FD&C Act, FDA expects sponsors to submit a request for Breakthrough Device designation prior to submission of the marketing application. FDA will not consider requests for designation contained within a marketing submission or submitted after a marketing submission has been received.

b. Multiple Devices with Same Intended Use

Breakthrough Device designation may be granted for multiple devices with the same proposed intended use, and a Breakthrough Device designation will not be revoked solely on the basis of another designated device obtaining marketing authorization.[41] As a consequence, multiple Breakthrough Device designations for the same intended use may be granted and have subsequent submissions pending simultaneously. However, when a Breakthrough Device has been approved or cleared or has had a De Novo request granted, no additional devices with the same intended use will be designated as a Breakthrough Device, unless the criteria for designation described above are still met in light of the first

[38] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-preference-information-voluntary-submission-review-premarket-approval-applications.
[39] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/principles-selecting-developing-modifying-and-adapting-patient-reported-outcome-instruments-use.
[40] Section 515B(c) of the FD&C Act (21 U.S.C. 360e-3(c)).
[41] See section 515B(d)(3) of the FD&C Act (21 U.S.C. 360e-3(d)(3)).

Breakthrough Device's market availability.

For example, Devices X and Y were accepted into the Breakthrough Devices Program after FDA determined for each device (1) that there was a reasonable expectation it could provide for more effective treatment of a life-threatening disease and (2) that it represented a breakthrough technology and offered significant advantages over existing approved or cleared alternatives. A De Novo request was later granted for Device X, allowing marketing of the device. FDA will not revoke the Breakthrough Device designation for Device Y, which is still pending premarket review after its designation, solely based on market availability of Device X.[42] However, Device Z, which has the same intended use as Device X, is now requesting designation as a Breakthrough Device on the basis of providing a significant advantage over Device X. Given that Device Z has the same intended use as Device X, Device Z may be eligible for Breakthrough Device designation only if it meets the designation criteria in light of the market availability of Device X.

Breakthrough Device designation will only be granted with respect to an intended use that meets the designation criteria described in Section 515B of the FD&C Act. Each request for a Breakthrough Device designation should include a description of only one proposed device and intended use, as well as a rationale for how the criteria are met.

c. Combination Products

Device-led combination products are eligible for Breakthrough Device designation. However, it is important to note that these products may raise unique scientific and regulatory challenges and issues. Further, it may not be possible to apply all of the policies described in this guidance to such combination products that receive Breakthrough Device designation due to such challenges and issues. Interactive review of complex issues requiring expertise from a different Center may require additional time to resolve. When CDRH or CBER receives a Q-Submission, IDE or marketing application for a device-led combination product that has been designated as a Breakthrough Device, CDRH or CBER intends to notify the consulting Center(s) of its receipt and include the appropriate review staff from the consulting Center(s) to ensure that the entire combination product review team is aware of the issues discussed and engaged, as needed, in the review.[43]

d. Reducing Disparities in Health and Health Care

Health and health care disparities exist and occur across many dimensions, including race, ethnicity, socioeconomic status, age, sex, disability status, sexual orientation, language, and location, among others, as summarized in reports by the Agency for Healthcare Research and Quality and Department of Health and Human Services Office of Minority Health as well as FDA

[42] See Section 515B(d)(3) of the FD&C Act (21 U.S.C. 360e-3(d)(3)).

[43] While the lead Center is the primary contact point for combination product sponsors, the Office of Combination Products (OCP) is available to participate in meetings or otherwise engage on regulatory matters for these products upon request (see section 503(g)(8) of the FD&C Act, 21 U.S.C. 353(g)(8)). For further information on combination products and OCP, see the OCP webpage at https://www.fda.gov/combination-products.

guidances.[44,45,46] Addressing health and health care disparities is not only important for achieving health equity,[47] but also for improving the overall quality of life and health outcomes for all patients. FDA recognizes the urgent public health need for innovative technologies that help to reduce barriers to achieving health equity and help to improve health outcomes across diverse populations. When assessing eligibility for the Breakthrough Devices Program using the statutory designation criteria,[48] FDA intends to consider technologies and device features that may help to address health and/or health care disparities and promote health equity by providing for more effective treatment or diagnosis in populations that exhibit health and health care disparities.

One dimension contributing to health and health care disparities is the inability to recognize and address the ways in which treatment outcomes may differ by race, ethnicity, sex, age, disability, and/or other factors. For some diseases, the pathophysiology, clinical features, and response to treatment may be impacted by these factors.[49] For example, differences in health outcomes may exist for pediatric and geriatric patients due to age-related physiologic changes. Health and health care disparities can be exacerbated due to a lack of recognition of these differences, including implicit biases, and/or the lack of devices designed to effectively diagnose or treat the condition in a manner that addresses these differences. The Breakthrough Devices Program can be used to help provide more timely access to devices that address the unmet needs of populations that may experience health and/or health care disparities. FDA considers technologies and device features tailored to address characteristic differences, such as those arising from social factors, phenotypic variations, pathophysiology, and/or response to treatment, when evaluating if there is a reasonable expectation that the device may provide for more effective treatment or diagnosis as compared to the current standard of care, including the device's potential to be more effective in certain populations. For example, as part of FDA's assessment of whether a device is reasonably expected to be more effective, we consider if it is designed to address a pathophysiological or clinical characteristic associated with certain populations that could have a clinically meaningful impact for the treatment or diagnosis of the condition in those populations. Such a device may, therefore, be considered as reasonably expected to offer a more effective treatment or diagnosis as is consistent with criterion 1 of the designation criteria.

Similarly, health and/or health care disparities may also arise in populations impacted by life-threatening or irreversibly debilitating diseases or conditions that are rare, such as sickle cell disease. In some cases, patients living with these rare diseases or conditions may have limited diagnostic and treatment options.

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[44] Refer to the 2021 National Healthcare Quality and Disparities Report available from: https://www.ahrq.gov/sites/default/files/wysiwyg/research/findings/nhqrdr/2021qdr.pdf.

[45] As described in the 2015 Report to Congress on Minority Health Activities available from: https://www.minorityhealth.hhs.gov/omh/browse.aspx?lvl=2&lvlid=57.

[46] For more information on the evaluation and reporting of race-specific, ethnicity-specific, and age-specific data, please see the FDA guidance "Evaluation and Reporting of Age-, Race-, and Ethnicity-Specific Data in Medical Device Clinical Studies," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/evaluation-and-reporting-age-race-and-ethnicity-specific-data-medical-device-clinical-studies. For more information on the evaluation of sex-specific data, please see the FDA guidance "Evaluation of Sex-Specific Data in Medical Device Clinical Studies," available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/evaluation-sex-specific-data-medical-device-clinical-studies-guidance-industry-and-food-and-drug.

[47] For purposes of this guidance, the Agency defines health equity according to the World Health Organization definition as the absence of unfair, avoidable and remediable differences in health status among groups of people. See Health equity and its determinants; World Health Organization; 2021; available from: https://cdn.who.int/media/docs/default-source/world-health-day-2021/health-equity-and-its-determinants.pdf?sfvrsn=6c36f0a5_1&download=true.

[48] As defined in section 515B(b) of the FD&C Act (21 U.S.C. 360e-3(b)).

[49] As described in the 2003 report from the Institute of Medicine (US) Committee on Understanding and Eliminating Racial and Ethnic Disparities in Health Care titled Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care available from: https://pubmed.ncbi.nlm.nih.gov/25032386/.

FDA considers technologies and device features tailored to address unmet needs in these populations when evaluating if there is a reasonable expectation that the device may provide for more effective treatment or diagnosis.[50]

Another major dimension of health and health care disparities is accessibility to quality health care. For the purposes of this guidance, we define accessibility as an individual or group's capacity to benefit from a medical device or procedure. This is distinct from use of the term "access" elsewhere in the guidance, which refers to commercial availability of a medical device following marketing authorization. Certain barriers, such as inequities in the availability of medical care, may prevent underserved populations from receiving medical treatment or diagnosis. Often the benefit of a device cannot be realized due to this lack of accessibility. New devices that have the potential to offer a clinically meaningful impact through improved accessibility may provide a significant benefit to patients by, for example, including user features that are adaptable or more easily used by diverse populations or allow for use in more diverse settings. As described in Section III.B.1.a of this guidance, when determining whether a device is reasonably expected to "provide for more effective treatment or diagnosis," FDA considers the totality of available information regarding the device, including its potential for a clinically meaningful impact and its potential benefits and risks. Therefore, when evaluating the first Breakthrough criterion, FDA intends to consider technologies and device features that could allow for improved accessibility when evaluating if there is a reasonable expectation that the device may provide for more effective treatment or diagnosis as compared to the current standard of care. For example, improved accessibility of a device may support that the device is reasonably expected to be more effective if there is information supporting its use in diverse settings such that a patient population with limited or no available options may have improved adherence to a prescribed medical regimen.[51]

C. Designation Review Process

A request for Breakthrough Device designation should be submitted as a "Designation Request for Breakthrough Device" Q-Submission. The procedures for submitting a Q-Submission to FDA are outlined in the FDA guidance, "Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program."[52] These Breakthrough Device designation requests are not subject to an acceptance review. An example approach[53] for a request for Breakthrough Device designation is provided in **Appendix 1: Illustrative Example: Breakthrough Device Designation Request**. The designation request should be the only request contained in the Q-Submission. Other Q- Submission topics should be submitted separately. This will help FDA meet the statutory timeframe for making a decision on a Breakthrough Device designation request. Furthermore, if sponsors are pursuing Breakthrough Device status and at the same time have other requests for feedback, they may wish to consider submitting the questions after FDA renders a designation decision. This is because the Breakthrough Device status may impact the feedback FDA provides. In addition, note that designation

[50] Consistent with section 515B(c) of the FD&C Act, Breakthrough Device designation may be requested at any time prior to the submission of a PMA, 510(k), or De Novo request. Sponsors should only request Breakthrough Device designation if they intend to pursue one of these marketing pathways. Other marketing pathways (e.g., Humanitarian Device Exemption) are not eligible for consideration under the Breakthrough Devices Program.

[51] Consistent with the goals of promoting the development of impactful devices, FDA considers this potential for increased benefit to patients to satisfy the "more effective treatment or diagnosis" criterion when evaluating a Breakthrough Designation request. These considerations for determining eligibility to participate in the program are different from and do not change the statutory requirements for safety and effectiveness to support a marketing authorization.

[52] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program.

[53] Section 515B(f)(1)(B) of the FD&C Act (21 U.S.C. 360e-3(f)(1)(B)) indicates that this guidance shall "provide a template for requests under subsection (c)." The illustrative appendix provides an example approach.

should be requested *separately* from the submission of a marketing submission or IDE application.

Please note that FDA may identify devices that may be good candidates for the Breakthrough Devices Program and recommend that sponsors of such devices consider applying to the program.

FDA will issue a grant or denial decision for each Breakthrough Device designation request within 60 calendar days of receiving such a request.[54] In general, FDA intends to interact with a sponsor by Day 30 regarding any requests for additional information needed to inform the designation decision. It is helpful when a sponsor is available and responsive to FDA requests throughout the review timeline. If FDA does not receive additional information needed to make a decision on a designation request in a timely manner, it may result in denial of the Breakthrough Device designation request.

Subject to the confidentiality provisions of the FD&C Act and implementing regulations, including FDA's Part 20 regulations covering information disclosure (21 CFR part 20),[55] and the Freedom of Information Act (FOIA) (5 U.S.C. 552),[56] FDA generally will not disclose the existence of requests for Breakthrough Device designation and our decisions on such designation requests. However, in certain cases, FDA may publicly disclose a Breakthrough Device designation that has been previously publicly disclosed or acknowledged by the sponsor of the Breakthrough Device designation request. Additionally, once a designated Breakthrough Device obtains marketing authorization for an indication consistent with its Breakthrough Device designation, FDA intends to publicly disclose its Breakthrough Device designation status for that indication for use.[57] Because Breakthrough Device designation is granted for a device and its indication for use, if a designated Breakthrough Device receives marketing authorization for an indication other than the indication covered by its designation, it is not considered a market-authorized Breakthrough Device and would not be disclosed as such.

D. Designation Withdrawal

A sponsor may request to withdraw from the Breakthrough Devices Program at any time. Such a request should be submitted in writing to FDA as a withdrawal amendment to the Q-Submission under which designation was granted.

FDA will not withdraw designation on the basis of another Breakthrough Device or a device given priority review under former section 515(d)(5) of the FD&C Act (as in effect prior to the date of

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[54] See section 515B(d)(1) of the FD&C Act (21 U.S.C. 360e-3(d)(1)). FDA's decision on a request for designation as Breakthrough Device constitutes a "significant decision" under section 517A of the FD&C Act (21 U.S.C. 360g-1), as amended by section 3051 of the Cures Act. Additional information regarding CDRH's interpretation of section 517A and the procedures applicable to a request for review of a significant decision by CDRH under section 517A is available in the respective FDA guidances, "Center for Devices and Radiological Health Appeals Processes: Questions and Answers about 517A" available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/center-devices-and-radiological-health-cdrh-appeals-processes-questions-and-answers-about-517a and "Center for Devices and Radiological Health (CDRH) Appeals Processes" available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/center-devices-and-radiological-health-cdrh-appeals-processes. For more information regarding the CBER appeals processes, please refer to the FDA guidance, "Formal Dispute Resolution: Sponsor Appeals Above the Division Level" available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/formal-dispute-resolution-sponsor-appeals-above-division-level-guidance-industry-and-review-staff.

[55] 21 CFR part 20 available at https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-20.

[56] Additional information related to FDA's implementation of the Freedom of Information Act can be found at https://www.fda.gov/regulatory-information/freedom-information/foi-information.

[57] FDA's Breakthrough Devices Program webpage is available at: https://www.fda.gov/medical-devices/how-study-and-market-your-device/breakthrough-devices-program. This webpage includes a listing of Breakthrough Devices that have obtained marketing authorization.

enactment of the Cures Act) with the same intended use receiving PMA approval, having a De Novo request granted, or receiving clearance of a 510(k).[58] However, FDA may withdraw designation at any time upon written notice to the sponsor if FDA determines that:

- for other reasons, the device is no longer eligible for a Breakthrough Device designation according to the criteria outlined in section 515B(b) of the FD&C Act (21 U.S.C. 360e-3(b)), based on available information; or

- the information submitted in support of a request for Breakthrough Device designation, including, without limitation, the designation request package or any related premarket submission, contained an untrue statement of material fact or omitted material information, including false statements relating to data collection.

IV. Program Features

The novelty of a Breakthrough Device can present key challenges because both the sponsor and FDA may face more uncertainty about how best to evaluate the device's safety and effectiveness. To expedite the development of these devices, FDA intends to offer sponsors a menu of options that offer opportunities for early and regular interaction with FDA as device development unfolds. A sponsor who wishes to request feedback on a device that has been designated as a Breakthrough Device may select one or more of the options described below in Sections A-D at any time prior to submitting a marketing application for that device; the sponsor need not, however, pursue any of these options. We consider options A-C to be a subset of Pre- Submissions. When submitting a Q-Submission for a designated Breakthrough Device, sponsors should specify if they are requesting one of the special program features available to designated Breakthrough Devices (i.e., a sprint discussion (IV.A), review of a Data Development Plan (IV.B), or a Clinical Protocol Agreement (IV.C)). Additionally, sponsors of Breakthrough Devices also have the option to request feedback from FDA through mechanisms that are available for non-Breakthrough Devices and may submit more traditional Pre-Submissions whose scope is consistent with typical requests for feedback received through the Pre-Submission Program (Section IV.D). Sponsors of designated Breakthrough Devices requesting any of the options described in Sections A-D should follow the processes outlined in the Q- Submission Guidance and should identify the Q-submission in the cover letter as an "Interaction for Designated Breakthrough Device."

A. Breakthrough Device Sprint Discussion

To support sponsors needing timely resolution of potentially novel issues, FDA offers "sprint" discussions with the goal of reaching mutual agreement on a specific topic within a set time period (e.g., 45 days). The number, format, and duration of interactions within a sprint discussion may vary based on project needs and should be defined *a priori* by the sponsor and FDA. During a sprint discussion, the sponsor may provide additional information or revisions to initial proposals. The schedule of such interactions as well as the information and proposals to be discussed during the sprint discussion may be modified during the sprint discussion as agreed upon with FDA. To facilitate this intensive level of interaction, a sprint discussion should follow the parameters below. Points of disagreement that cannot be resolved quickly should be expeditiously elevated to senior management. In some cases, the sponsor may wish to consider FDA feedback after conclusion of the sprint discussion prior to determining whether disagreement exists and whether additional discussion is needed.

[58] See section 515B(d)(3) of the FD&C Act (21 U.S.C. 360e-3(d)(3)).

(1) Single Topic with Specific Goals

To allow for a detailed discussion and timely resolution, a sprint should have only one general topic (e.g., animal study protocol design, strategy for focused non-clinical testing, clinical protocol discussion, statistical analysis plan review) and specific goals (e.g., determine primary and secondary endpoints for pivotal study). In a sprint discussion request, a sponsor should propose a topic and goals(s). FDA may work with the sponsor to refine the topic, timeline and goal(s) as needed. It is generally recommended that a sponsor have no more than one sprint discussion open at a time. This will allow both FDA and the sponsor to devote sufficient resources to support a highly interactive, collaborative, and dynamic sprint process.

(2) Defined Interaction Schedule, Including Planned Participants

Sprint discussion requests are not subject to the acceptance review described in the Q- Submission Guidance. A sponsor should propose an interaction schedule and a defined end date (e.g., 45 days). FDA will propose revisions to the timeline, if needed, with the goal of reaching agreement on the timeline early in the sprint review. In general, FDA anticipates providing feedback on sprint issues in less time than would be expected for a traditional Pre-Submission. Since progress may require the presence of key individua ls at meetings during the sprint discussion, the sponsor should propose its planned attendees (e.g., regulatory manager, animal study consultant, clinical consultant) and, as relevant, request FDA attendees with specific expertise (e.g., animal study reviewer, clinician, statistician).

The sprint discussion is intended to be highly interactive, and FDA understands that, based on an early interaction, the sponsor may choose to provide additional information to FDA to support later interactions for the sprint. If the sponsor provides new information to FDA during the sprint, FDA will attempt to incorporate the information into its review and feedback while still adhering to the agreed-upon timeline. However, depending on the extent of the new information provided and the time remaining for the review, revisions to the timeline may be needed.

(3) Clear Documentation of Interactions and Conclusions

FDA will provide summary feedback to the sponsor after the close of a sprint discussion. This summary should include the points of agreement, points of disagreement, if any, and points necessitating further discussion. To facilitate any review of new or revised information provided during the sprint, it is recommended that the sponsor provide “track changes” versions of any revised documents and/or clearly indicate with a summary table or timeline what changes or new information is being or has been provided. At the conclusion of the sprint discussion, the sponsor should develop draft minutes and provide the draft minutes as an amendment to the relevant Pre- Submission. Timing for submission of draft meeting minutes should be addressed in the sprint discussion schedule.

FDA intends that feedback the Agency provides in response to a sprint discussion will not change, provided that the information submitted in a future IDE or marketing application is consistent with that provided in the sprint submission and that the data in the future submission do not raise any important new issues materially affecting safety or effectiveness. FDA intends that modifications to its feedback be limited to situations in which FDA concludes that the feedback given previously does not adequately address important new issues materially relevant to a determination of safety or effectiveness that have emerged since the time of the sprint discussion. For example, FDA may modify its previous feedback if

new scientific findings emerge that indicate there is a new risk or an increased frequency of a known risk that affects FDA's prior advice, or if there is a new public health concern that affects FDA's prior advice. In such cases, FDA will acknowledge a change in the advice and will document clearly the rationale for the change, and the changed advice will be supported by the appropriate managerial concurrence.

Sponsors should recognize that even though the Agency may have already reviewed the sponsor's protocols/plans in a sprint discussion, this does not guarantee approval, clearance, or granting of future submissions. Additional questions may be raised during the review of the future submission when all information is reviewed and considered as a whole. Although sprint discussions are not decisional or binding on the Agency or the sponsor, it is FDA's intent to provide the best advice possible based on the information provided and other information known at that point in time.

(4) Supporting Materials

To enable quick, efficient discussion of the sprint topic, it is important that the sponsor provide FDA with, and clearly reference, all materials needed to support review and interaction (e.g., a submission might contain an appendix with a draft protocol). FDA recommends that sponsors provide a rationale justifying their proposed approach within their supporting materials to best facilitate review and interactions.

(5) Example Sprint Discussion

The example sprint discussion below incorporates the concepts discussed above:

- On Day 7, following receipt of the submission, FDA and the sponsor hold an informational discussion to walk FDA through the sponsor's materials and questions. During this meeting, FDA and the sponsor discuss an interaction schedule to facilitate collaboration and overall topics and goals for sprint interactions.

- On Day 14, FDA emails the sponsor with initial feedback and questions for upcoming discussion.

- On Day 21, FDA and the sponsor meet (via teleconference or face to face) to discuss FDA's initial feedback and questions. FDA and the sponsor discuss initial approaches for addressing any outstanding issues.

- On Day 28, based on the feedback received and the prior discussion, the sponsor provides additional information or revised supporting materials to FDA via email in response to outstanding issues.

- On Day 35, FDA and the sponsor meet via teleconference to discuss the revised supporting materials provided by the sponsor. Based on this discussion, FDA and the sponsor identify substantive areas of agreement and points necessitating further discussion, if any. The sponsor may wish to consider FDA feedback prior to determining whether agreement or disagreement exists and whether additional discussion is needed. However, if any substantive points of disagreement are identified by FDA or the sponsor at this point, FDA develops a plan for how senior management will be involved to support quick resolution of the identified issues (see Section II.E above) which may include early notification of the potential need for their involvement.

- On Day 40, the sponsor provides via email draft minutes from previous discussions including substantive points of agreement, points necessitating further discussion or points of disagreement, if any.

- On Day 45, FDA provides any edits to meeting minutes, including substantive points of agreement and points necessitating further discussion, if any. If there are no points of disagreement, FDA will close out the sprint discussion. If points of disagreement exist, FDA will proceed with the plan for senior management involvement to quickly address the outstanding issues, which might include a teleconference involving senior management by Day 50.

B. Data Development Plan (DDP)

Sponsors of Breakthrough Devices may request coordination with FDA regarding a Data Development Plan (DDP). The DDP is a high-level document intended to help ensure predictable, efficient, transparent, and timely device assessment and review by outlining data collection expectations for the entire product lifecycle. It should describe the balance of premarket and, as applicable, postmarket collection of clinical and non-clinical data. FDA intends to work with the sponsor so that the plan is developed in a manner that is least-burdensome and predictable, while allowing for some measure of flexibility and adjustments as appropriate. While the optimal timeframe for submission of a DDP will vary depending on the device, and is ultimately at the sponsor's discretion, it may be most beneficial to initiate DDP discussions with FDA soon after a Breakthrough Device designation has been granted.

An example approach to a DDP can be found in **Appendix 2: Data Development Plan (DDP) Example Approach.**

Importantly, the DDP may include both clinical and non-clinical testing approaches. In FDA's experience, sponsors often focus on clinical study design but tend to overlook potential hurdles raised by non-clinical issues. FDA encourages sponsors to consider the non-clinical testing that will be needed to support the regulatory review of their device early on and to discuss the planned approach with FDA. The DDP should discuss the non-clinical testing that would be conducted and the timing of such testing relative to planned clinical studies and a subsequent marketing application. It may be appropriate for clinical testing to begin based upon preliminary non-clinical results or with some non-clinical testing deferred, depending on the mitigations in place to protect study subjects. Please note that FDA and the sponsor may wish to discuss a complete DDP with all planned clinical and non-clinical testing for pre- and postmarket data collection, if appropriate, or a component or subset of the DDP (e.g., premarket non-clinical testing assessment plan).

FDA review of a DDP may follow a similar model as the sprint discussion described above and is not subject to an acceptance review. In general, FDA anticipates that feedback on a DDP will be provided in less time than would be expected for a traditional Pre-Submission.

C. Clinical Protocol Agreement

As described in section 515B(e)(2)(D) of the FD&C Act (21 U.S.C. 360e-3(e)(2)(D)), the Breakthrough Devices Program includes a provision for obtaining agreement in writing for clinical protocols, which will be considered binding on both FDA and the sponsor, subject to the following:

- Any changes to the previously agreed-upon protocol are agreed upon in writing by both

FDA and the sponsor; or

- The director of the Office responsible for reviewing the device determines that a substantial scientific issue essential to determining the safety or effectiveness of the device exists. In this case, the director's decision must be provided in writing and can be made only after FDA has provided an opportunity to the sponsor to meet and discuss the substantial scientific issue(s). Such a meeting would need to include the Office director and clearly document the substantial scientific issue(s) discussed.

As with the sprint discussion and DDP features described above, a request for a clinical protocol agreement is not subject to an acceptance review. FDA will work interactively with sponsors who choose to pursue a clinical protocol agreement. Upon reaching agreement, FDA will issue a letter documenting the agreement reached.

D. Other Pre-Submission for Designated Breakthrough Device

FDA recognizes that some sponsors of devices designated as Breakthrough Devices may wish to engage with FDA on multiple topics in a single Pre-Submission rather than utilize one of the options presented above in Section IV.A-C. For these types of requests for feedback, the sponsor may submit a Pre-Submission as described in the Q-Submission Guidance[59] and request that it be tracked as an "Interaction for Designated Breakthrough Device" in the cover letter. Review teams will prioritize these submissions and develop a timeline for feedback with the sponsor, consistent with commitments specified as part of the Medical Device User Fee Amendments of 2017.[60]

E. Regular Status Updates

FDA and the sponsor of a Breakthrough Device may agree to have regular (e.g., bimonthly) status updates. Through these interactions, FDA and the sponsor may discuss general progress of the project (e.g., timeframe for a planned marketing submission) and next steps or plans for future discussions. These interactions may be by email, virtually (by videoconference or teleconference), or in-person (face-to-face), as agreed upon by FDA and the sponsor. These interactions may be between the primary FDA and sponsor contacts (e.g., FDA lead reviewer) or may include additional participants as needed including FDA managers. Regular status updates provide an opportunity for a high-level view of the project and identification of potential hurdles, while a sprint discussion provides the opportunity for detailed feedback to address specific sponsor goals. A Pre-Submission is not recommended or needed for status updates.

[59] Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program.

[60] See 163 CONG. REC. S4729-S4736 (daily ed. August 2, 2017) (Food and Drug Administration User Fee Reauthorization), also available at https://www.fda.gov/industry/medical-device-user-fee-amendments-mdufa/medical-device-user-fee-amendments-2017-mdufa-iv.

Appendix 1: Illustrative Example: Breakthrough Device Designation Request

This appendix provides an example of information that may be helpful to include in a request for designation into the Breakthrough Devices Program.

Background Information

Device Description: This section provides an overview of the product, including principles of operation (including device and/or drug components) and properties relevant to clinical function, if known. Images or engineering schematics are also encouraged for inclusion, as appropriate.

Indications for Use: This section presents indications for use for which you are requesting designation. The indications for use should clearly outline a patient population that meets the designation criteria.[61]

Regulatory History: This section details the history of previous FDA interactions and submissions, including feedback received and resolution of that feedback, as applicable. All relevant IDE, 513(g),[62] and Q-Submission numbers should be included.

Designation Criteria

Criterion 1: Device "provides for more effective treatment or diagnosis of life-threatening or irreversibly debilitating human disease or conditions."[63]

This section provides a discussion regarding how the first designation criterion is met by the proposed device and indications for use.

Criterion 2: Device meets one of the components of the criterion, listed below:

(A) Device "represent[s] breakthrough technolog[y];"[64]

(B) "[N]o approved or cleared alternatives exist;"[65]

(C) Device "offer[s] significant advantages over existing approved or cleared alternatives, including the potential, compared to existing approved alternatives, to reduce or eliminate the need for hospitalization, improve patient quality of life, facilitate patients' ability to manage their own care (such as through self-directed personal assistance), or establish long term clinical efficiencies;"[66] *or*

(D) Device availability "is in the best interest of patients."[67]

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[61] See section 515B(b) of the FD&C Act (21 U.S.C. 360e-3(b)).
[62] See FDA Guidance "FDA and Industry Procedures for Section 513(g) Requests for Information under the Federal Food, Drug, and Cosmetic Act" available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-and-industry-procedures-section-513g-requests-information-under-federal-food-drug-and-cosmetic.
[63] See section 515B(b)(1) of the FD&C Act (21 U.S.C. 360e-3(b)(1)).
[64] See section 515B(b)(2)(A) of the FD&C Act (21 U.S.C. 360e-3(b)(2)(A)).
[65] See section 515B(b)(2)(B) of the FD&C Act (21 U.S.C. 360e-3(b)(2)(B)).
[66] See section 515B(b)(2)(C) of the FD&C Act (21 U.S.C. 360e-3(b)(2)(C)).
[67] See section 515B(b)(2)(D) of the FD&C Act (21 U.S.C. 360e-3(b)(2)(D)).

This section provides a discussion of which component(s) of Criterion 2 is/are met by the proposed device and indications for use. Please note that multiple components may apply; however, only one of these components must be met. For each component of Criterion 2 identified as being met, a discussion regarding how that component is met should be included.

Relevant patient preference information[68] may be included to support that a device and indications for use meet Criteria 1 and 2 above. Relevant patient preferences could be based on attributes of the device type and/or patient population, or the specific device under review.
Examples include, but are not limited to:

- information that captures relative desirability or acceptability of outcomes or other attributes that differ among alternative health interventions to patients, or the value patients place on the treatment or diagnosis;
- patient tolerance of risk to achieve benefit (e.g., given disease severity, chronicity);
- how well patients are able to understand the benefits and risks; or
- any other relevant patient-centric assessments.

What is the planned marketing application?

- *PMA;*
- *De Novo request; or*
- *510(k).*

This section provides a discussion of which marketing application you plan to submit for your device, including a rationale for your selection. Only one application type should be selected.

[68] For additional information, please see the FDA 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" available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-preference-information-voluntary-submission-review-premarket-approval-applications.

Appendix 2: Data Development Plan (DDP) Example Approach

This appendix provides an example of information found to be helpful in a Data Development Plan (DDP).

Background Information

Device Name: Name of the device.

Device Description: Overview of the product, including principles of operations (including device components) and properties relevant to clinical function, if known. Images or engineering schematics are also encouraged for inclusion, as appropriate.

Indications for Use: Indications for use for which designation was granted (see **Appendix 1: Illustrative Example: Breakthrough Device Designation Request**).

Data Collection Plan

The tables below present example approaches to consider for identifying the planned non-clinical testing and clinical studies.

Non-clinical Test	**Reference Standard, Method, Acceptance Criteria, Objective, etc.**	**Timeline**
Test name/type. *Examples: Electromagnetic compatibility, biocompatibility, sterilization, mechanical fatigue testing, animal study,*[69] *address disapproval concerns #1-10 in FDA's G160001 letter dated 1/31/2016.*	Relevant standard, description of method, acceptance criteria, objective, etc. to describe testing expectations. *Examples: IEC 60601-1-2; cytotoxicity, sensitization, and irritation testing per ISO 10993; assess operability of device; see disapproval concern language.*	When test results should be provided to FDA. *Examples: In feasibility study IDE, in pivotal study IDE, in marketing application, in postapproval study.*

[69] FDA supports the principles of the "3Rs," to replace, reduce, and/or refine animal use in testing, when feasible. We encourage sponsors to consult with us if it 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.

Clinical Study Type of clinical study. Note that this table should be repeated for each clinical study. *Examples: early feasibility, feasibility, stage I pivotal, stage II pivotal, pivotal, postapproval.*	
Purpose	Purpose of study. *Examples: To demonstrate basic safety and proof of principle for XXXXX device; to demonstrate superiority to control with respect to surrogate endpoints; to confirm adequacy of surrogate endpoints in prediction of mortality and morbidity benefit.*
Study Design	Study design information. *Examples: Single-center, nonrandomized; multi-center randomized, double-blinded.*
Study Population	Study population, which should align with indications for use requested. *Example: Patients with upper extremity and lower extremity spasticity secondary to stroke, who meet all other study inclusion criteria and none of the study exclusion criteria.*
Inclusion Criteria	Inclusion criteria. *Examples: Patients over 18 years of age, on optimal medical therapy, and who have had symptoms for >3 months; to be determined pending feasibility study result but will align with requested indications for use.*
Exclusion Criteria	Exclusion criteria. *Examples: Patients eligible for physical therapy or surgery, unable to provide informed consent, enrolled in clinical study for same condition; to be determined pending feasibility study results but will align with requested indications for use.*
Safety Endpoints	Safety endpoints. *Example: No statistically-based safety endpoint, but the below adverse events will be captured; treatment-related adverse events as defined below <30%>.*
Effectiveness Endpoints	Effectiveness endpoints. *Examples: No statistically-based effectiveness endpoint, but the following parameters will be captured; patient success defined as improvement of ≥2 points on Quality of Life (QOL) scale and study success defined as >75% patients meeting success criteria; to be determined based on effect size estimates from feasibility study.*

Follow-Up Schedule	Follow-up schedule. *Example: Subject participation will last approximately 4 weeks as indicated below, adverse events will be captured throughout study, Week 1: enrollment, informed consent, baseline assessment, Week 2: procedure, Week 3: electrical parameter collection and QOL assessment, Week 4: electrical parameter collection and QOL assessment, study exit; to be determined based on feasibility study results.*