

The 21st Century Cures Act (Cures), signed into law on December 13, 2016, amended several sections of the Federal Food, Drug, and Cosmetic Act. This guidance was developed and issued prior to the enactment of Cures, and certain sections of this guidance may no longer be current as a result. FDA is assessing how to revise this guidance to represent our current thinking on this topic. For more information please contact CDRH-Cures@fda.hhs.gov.

Expedited Access for Premarket Approval and *De Novo* Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Diseases or Conditions

Guidance for Industry and Food and Drug Administration Staff

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**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

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Guidance for Industry and Food and Drug Administration Staff

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. Introduction

The Food and Drug Administration (FDA or the Agency) is introducing a new, voluntary program for certain medical devices that demonstrate the potential to address unmet medical needs for life threatening or irreversibly debilitating diseases or conditions and are subject to premarket approval applications (PMAs) or *de novo* requests. FDA believes that the “Expedited Access Pathway for Unmet Medical Needs for Life Threatening or Irreversibly Debilitating Diseases or Conditions” (“Expedited Access Pathway” or “EAP”) program will help patients have more timely access to these medical devices by expediting their development, assessment, and review, while preserving the statutory standard of reasonable assurance of safety and effectiveness for premarket approval¹ and the statutory standards for granting a *de novo* request² consistent with the Agency’s statutory mission to protect and promote public health.

¹ See section 515(d) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

² See section 513 of the FD&C Act.

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In some cases, patients may be willing to assume greater risk for earlier access to a medical device. This may be particularly true for patients with conditions for which no treatments exist or those who face serious or life-threatening conditions. FDA must ensure that if access to medical devices is expedited, FDA is reasonably assured the device is safe and effective. Reducing premarket data requirements while increasing postmarket requirements for devices subject to a PMA, when appropriate, can assist FDA in making medical devices available to patients sooner than if following the traditional premarket review pathway. Devices eligible for this pathway include new devices and existing devices for which a new indication is sought or when there is a change or modification in the device that could significantly affect the safety and effectiveness of the device [21 CFR 807.81(a)(3)(1)].

As part of this EAP program, FDA intends to provide, as resources permit, more interactive communications during device development and more interactive review of Investigational Device Exemptions (IDEs), PMA applications, and *de novo* requests. In addition, FDA intends to work interactively with the sponsor to create a data development plan specific to the device (“Data Development Plan”). The Data Development Plan should outline all data the sponsor intends to collect in support of device approval,³ including what data will be collected premarket and postmarket.

FDA’s EAP program contains features from CDRH’s Innovation Pathway, piloted in 2011 to facilitate the development and expedite the review of breakthrough technologies.⁴ In addition, the EAP program is based in part on FDA’s experience with the Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) programs that are intended to facilitate and expedite development and review of new drugs to address unmet medical needs in the treatment of serious or life-threatening conditions (“FDA drug expedited programs”).⁵ However, while the EAP program incorporates some features of the drug expedited programs, it is a separate and distinct program tailored to devices and intended to further speed the availability of certain safe and effective medical devices that address unmet public health needs. Combination products may raise unique scientific and regulatory challenges. Sponsors intending to pursue approval of a combination product for which the device component may qualify for EAP designation should discuss the feasibility of using the EAP pathway with FDA as early as possible.

FDA’s guidance documents, including this one, do not establish legally enforceable responsibilities. Instead, guidance documents describe the Agency’s current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory

³ For purposes of this guidance document, “approval” may refer to PMA approval or granting a *de novo* request.

⁴ For a description of the Innovation Pathway, see FDA’s Innovation Pathway webpage at <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHInnovation/InnovationPathway/default.htm>.

⁵ See FDA’s guidance “Expedited Programs for Serious Conditions – Drugs and Biologics,” issued May 2014, which discusses, among other things, the following CDER and CBER programs: Fast track designation, breakthrough therapy designation, accelerated approval, and priority review designation. See also sections 901 and 902 of the Food and Drug Administration Safety and Innovation Act (Pub. L. 112-144) and 21 CFR Part 314 Subpart H.

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requirements are cited. The use of the word *should* in Agency guidance documents means that something is suggested or recommended, but not required.

II. Background

Innovation Pathway

The EAP program contains features of the Innovation Pathway, such as earlier interactions between FDA and sponsors, and, where appropriate, senior management involvement and the use of a case manager.⁶ FDA launched the Innovation Pathway in 2011 to facilitate the development and expedite the review of breakthrough technologies. By engaging with innovators much earlier and more interactively during device development, we believe we can help reduce the time and cost of the entire process of bringing safe and effective technologies to patients.

The Innovation Pathway includes the development of an early, comprehensive plan for the device that outlined data collection needs as well as scientific and regulatory issues likely to surface during the review process, with the idea that subsequent communication between FDA and the sponsor would then be much smoother and more successful.

A key EAP program feature that is influenced by FDA's Innovation Pathway is the development of a Data Development Plan, which includes a description of the clinical and nonclinical data that the sponsor proposes to be collected, as well as a timeline for the development and marketing of the device. FDA believes that the Data Development Plan will help assure predictable, efficient, transparent, and timely device assessment and review.

By interacting with sponsors early and often throughout the review process, FDA and sponsors can better identify and address novel scientific issues earlier so as to expedite both device assessment and premarket review.

Role of Postmarket Data for EAP Devices Subject to a PMA

As part of the EAP program, FDA intends to work interactively with the sponsor within the benefit-risk framework discussed in the FDA guidance, "[Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approvals and De Novo Classifications](#)," issued on March 28, 2012 ("Benefit-Risk Guidance"),⁷ and in accordance with statutory and regulatory requirements, to determine whether certain data may be collected postmarket rather than premarket.

⁶ See *Medical Device Innovation Initiative White Paper*, February 2011, available at <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHInnovation/ucm242067.htm#1>.

⁷ The Benefit-Risk Guidance is available at: <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM296379.pdf>.

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FDA's guidance entitled "Balancing Premarket and Postmarket Data Collection for Devices Subject to Premarket Approval,"⁸ issued on April 13, 2015, clarifies FDA's current policy on balancing premarket and postmarket data collection during FDA review of PMAs. More specifically, it outlines how FDA considers the role of postmarket information in determining the extent of data that should be collected in the premarket setting, while still meeting the statutory standard of reasonable assurance of safety and effectiveness.

Getting the right balance between premarket and postmarket data collection – specifically, where appropriate, a greater reliance on postmarket collection – can reduce the extent of premarket data submission and directly impact when patients will have access to high-quality, safe and effective medical devices.

Section 513(a)(3)(C) of the FD&C Act requires FDA to consider the use of postmarket controls in lieu of collecting and reviewing all effectiveness data prior to PMA approval.⁹ In addition, section 513(a)(3)(D)(ii) of the FD&C Act (the "least burdensome provision") specifically provides:

Any clinical data, including one or more well-controlled investigations, specified in writing by the Secretary for demonstrating a reasonable assurance of device effectiveness shall be specified as a result of a determination by the Secretary that such data are necessary to establish device effectiveness. The Secretary shall consider, in consultation with the applicant, the least burdensome appropriate means of evaluating device effectiveness that would have a reasonable likelihood of resulting in approval.

The consideration of postmarket information as part of premarket review is discussed in FDA's Benefit-Risk Guidance as one of the principal factors that FDA considers when making benefit-risk determinations during the premarket review for devices subject to PMA,¹⁰ and is consistent with FDA's guidance entitled, "[The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles](#)" ("Least Burdensome Guidance"), issued October 4, 2002.¹¹

⁸ See FDA's guidance, "Balancing Premarket and Postmarket Data Collection for Devices Subject to Premarket Approval" (<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM393994.pdf>).

⁹ Specifically, section 513(a)(3)(C) states: "In making a determination of a reasonable assurance of the effectiveness of a device for which [a premarket approval application] has been submitted, the Secretary shall consider whether the extent of data that otherwise would be required for approval of the application with respect to effectiveness can be reduced through reliance on postmarket controls."

¹⁰ Under section 513(a) of the FD&C Act, FDA determines whether PMAs provide a "reasonable assurance of safety and effectiveness" by "weighing any probable benefit to health from the use of the device against any probable risk of injury or illness from such use," among other relevant factors.

¹¹ Available at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm085994.htm>. As discussed in the Least Burdensome Guidance, the role of postmarket information should be considered in determining the appropriate type and amount of data that should be collected in the premarket setting to support premarket approval. Postmarket information should also be considered for assuring long-term device safety and effectiveness, wherever appropriate. Reliance on postmarket controls (e.g., compliance with the Quality System

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We state in the Benefit-Risk Guidance:

FDA may consider the collection of postmarket data as a way to clarify the magnitude and effect of mitigations or as a way to develop additional information regarding benefits or risks for certain device types or in specific patient populations when making a benefit-risk determination. . . . In addition, pursuant to section 513(a)(3)(C) of the FD&C Act, in certain cases, such as if a device is likely to be denied approval due to uncertainty about its effectiveness, FDA will consider whether postmarket data collection or other conditions might be structured so as to permit approval subject to those conditions.¹²

As part of FDA's benefit-risk determination framework, FDA may also consider the degree of uncertainty of the probable benefits and probable risks of a device in the Agency's review of a PMA. As part of the uncertainty factor discussed in the Benefit-Risk Guidance, FDA states that:

there is never 100% certainty when determining reasonable assurance of safety and effectiveness of a device. However, the degree of certainty of the benefits and risks of a device is a factor we consider when making benefit-risk determinations.¹³

FDA recognizes that device approvals are not made with absolute certainty because of significant obstacles, such as the time and cost involved to address possible rare adverse events or long-term safety issues, and because controlled clinical studies do not fully represent the benefit-risk profile of a device when used in real-world clinical practice. Because devices that qualify for the EAP program ("EAP Devices") demonstrate the potential to address unmet medical needs for life threatening or irreversibly debilitating diseases or conditions, in order to help patients have more timely access to these medical devices, FDA may accept less certainty regarding the benefit-risk profile of EAP devices subject to a PMA at the time of premarket approval and approve an EAP Device as long as the data still support a reasonable assurance of safety and effectiveness. That is, FDA intends to approve an EAP Device subject to a PMA if the uncertainty is sufficiently balanced by other factors to support premarket approval (e.g., the probable benefits of the device, the probable benefits of earlier patient access to the device, and postmarket controls).

As part of the EAP program, FDA intends to impose postmarket requirements, including requiring post-approval studies as a condition of approval for devices subject to a PMA when applicable.¹⁴ The extent to which FDA will accept certain data to be collected for an EAP Device

regulations, post-approval studies, postmarket surveillance, and the Medical Device Reporting requirements) should be considered as a mechanism to reduce the extent of the premarket data for PMAs, while still ensuring that the statutory standard for premarket approval is met.

¹² See footnote 7.

¹³ See footnote 7.

¹⁴ 21 CFR 814.82 states: "FDA may impose post-approval requirements in a PMA approval order or by regulation at the time of approval of the PMA or by regulation subsequent to approval." In addition, under section 522 of the FD&C Act and FDA's implementing regulations at 21 CFR Part 822, FDA may order postmarket surveillance for certain Class III devices.

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in the postmarket setting, rather than premarket, is affected by the Agency's current authority to mandate completion of post-approval studies and to withdraw PMA approval for marketed devices for which FDA later determines that there is a lack of a showing of reasonable assurance that the device is safe or effective under the conditions of use prescribed, as well as by the current capabilities of FDA's medical device surveillance system. FDA would not offer a greater ability to collect postmarket benefit-risk data otherwise typically collected premarket for a *de novo* request (as we may for a PMA device) because once a *de novo* request is granted, the product can serve as a predicate for a device that need only demonstrate substantial equivalence for a 510(k) clearance. This would be problematic if we granted a *de novo* for a device that subsequently was shown not to be safe or effective based on required postmarket data collection.

As discussed in section III.G of this guidance, there are several actions that the sponsor or FDA may take in the postmarket setting as a result of the required conditions of approval for a PMA. For example, FDA may take enforcement action if the sponsor has not met the required conditions of approval, including failure to initiate or complete a post-approval study specified in the approval order for the device. In addition, FDA believes that the implementation of our 2012 strategy for a National Medical Device Postmarket Surveillance System entitled "Strengthening Our National System for Medical Device Postmarket Surveillance" could address certain limitations with the current medical device surveillance program and allow for a greater shift of premarket data collection to the postmarket setting for appropriate devices.¹⁵

III. Expedited Access Pathway

EAP is a new voluntary program for certain medical devices that demonstrate the potential to address unmet medical needs for life threatening or irreversibly debilitating diseases or conditions and are subject to PMAs or *de novo* requests. FDA believes that the EAP program will help patients have more timely access to these medical devices by expediting their development, assessment and review, while preserving FDA's statutory standard for PMA approval (reasonable assurance of safety and effectiveness) and the statutory standards for granting *de novo* requests.¹⁶

¹⁵ In September 2012, FDA released an initial report, "Strengthening Our National System for Medical Device Postmarket Surveillance," providing an overview of FDA's medical device postmarket authorities and the current U.S. medical device postmarket surveillance system and also proposed four specific actions, using existing resources and under current authorities, to strengthen the medical device postmarket surveillance system in the U.S. This report is available at:

<http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDRH/CDRHReports/UCM301924.pdf>. The update to the report, published in April 2013, detailed the concrete steps that the FDA intends to complete to more efficiently collect better and more timely data, helping to identify issues more quickly. This update is available at:

<http://www.fda.gov/downloads/MedicalDevices/Safety/CDRHPostmarketSurveillance/UCM348845.pdf>.

¹⁶ Criteria at section 513(a)(1)(A) or (B) of the FD&C Act are met. See also 513(f)(2)(A)(v) which states: "The person submitting the request for classification... may recommend to the Secretary a classification for the device and shall, if recommending classification in class II, include in the request an initial draft proposal for applicable special controls, as described in subsection (a)(1)(B), that are necessary, in conjunction with general controls, to provide reasonable assurance of safety and effectiveness and a description of how the special controls provide such assurance. Any such request shall describe the device and provide detailed information and reasons for the

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Participation in the EAP program is only at the request of the sponsor and with FDA's agreement. Because devices accepted into the EAP program demonstrate the potential to address unmet medical needs, FDA believes that it is in the interest of public health for patients to have earlier access to these devices. For example, EAP Devices may offer a potential for clinically meaningful benefit¹⁷ as compared to existing alternatives (preventative, diagnostic, or therapeutic) or provide a breakthrough technology over currently available legally marketed devices for patients with life-threatening or irreversibly debilitating diseases or conditions. Breakthrough technology includes novel technologies as well as novel applications of existing technologies. Examples include: expansion of the indications of cochlear implantation to patients with significant low-frequency residual hearing; the first drug-coated balloon catheter to treat vascular disease; a hemostatic device intended for internal use to temporarily control bleeding in the battlefield; an assay based on existing and commonly used technology (e.g., immunohistochemistry) if it provides a clinically meaningful advantage when used with a highly effective therapeutic; and, novel IVDs developed using next generation sequencing (NGS) technology.

Any reduction in data collection to support the decision to market should be consistent with principles discussed in this guidance. (See section III.D – Types of Clinical Evidence That May Support PMA Approval for EAP Devices.)

Through the EAP program, FDA intends to engage with sponsors of EAP Devices earlier and more interactively during the device's development, assessment and review. For example, FDA intends to work closely with sponsors of EAP Devices to develop a Data Development Plan for the device that provides, among other elements, a description of the premarket and postmarket data collection and an explanation and justification for the proposed balance of premarket and postmarket data collection (if applicable), with the goal of significantly reducing the time and cost from device development to FDA marketing decision, while still meeting the statutory standard of reasonable assurance of safety and effectiveness for PMA devices and the statutory standard for granting *de novo* requests (i.e., general controls or general and special controls support a classification of Class I or Class II, respectively). FDA intends to work interactively with sponsors during reviews of pre-submissions, IDEs, PMAs, *de novo* requests, and when other issues arise during the course of EAP Device development and assessment.

As part of the EAP program, the sponsor may use the types of clinical evidence that we discuss in section III.D of this guidance in support of approval (e.g., surrogate endpoints), but does not have to in order to participate in the EAP program. In addition, as part of the EAP program, on a case-by-case basis, FDA may, where appropriate, allow a sponsor to provide less manufacturing information in their PMA. In appropriate cases for PMA devices, FDA may also, at its discretion, forgo inspection of certain manufacturing sites and instead conduct those inspections after product approval (see section III.E of this guidance for further discussion). Finally, as discussed in section III.F of this guidance, FDA may impose certain postmarket requirements as

recommended classification. More information about the *de novo* process is available at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080195.htm>.

¹⁷ Clinically meaningful benefits include quantitative and qualitative benefits.

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part of the EAP program, including conditioning the approval of EAP Devices on continuing evaluation and periodic reporting on the safety, effectiveness, and reliability of these devices for their intended uses, in accordance with 21 CFR 814.82(a)(2), if, as part of the EAP program, FDA shifts data that would otherwise be collected premarket to the postmarket setting for PMA devices.

These postmarket data will enable the Agency to assess the risks and benefits of these devices with a higher degree of certainty and, if appropriate to protect patient safety, take appropriate postmarket action as described in section III.G below.

Included below are the criteria FDA considers when determining whether a device qualifies for the EAP program. This program includes a four-step process:

- (1) Request for designation as an EAP Device (“EAP Designation”),
- (2) Agreement on a Data Development Plan,
- (3) Review of a PMA or *de novo* request for an EAP Device, and
- (4) If approved and appropriate, postmarket data collection and evaluation.

Attachment 1 provides more discussion on the EAP Designation process and Attachment 2 provides the general elements that FDA recommends be included in the draft Data Development Plan. If FDA grants the EAP Designation, the sponsor may then work with FDA to further develop the sponsor’s Data Development Plan. FDA intends for the Data Development Plan to evolve during premarket development and review and for FDA and the sponsor to agree upon this Data Development Plan prior to submission of the PMA application or *de novo* request.

To be clear, *de novo* requests are not eligible for the full scope of the EAP program. The table below summarizes what aspects of the EAP program may be available to or required of sponsors of each type of submission.

EAP component	PMA	<i>De Novo</i>
Earlier and more interactive review with FDA staff, pending available resources [see Section III.B(1)]	Yes	Yes
Data Development Plan [see Section III.A(3) and Attachment 2]	Yes	Yes
Priority Review [see Section III.B(4)]	Yes	Yes ¹⁸
Clinical Evidence (see Section III.D)	Yes	No
Manufacturing (see Section III.E)	Yes	No
Conditions of Approval (see Section III.F)	Yes	No
Postmarket Actions (see Section III.G)	Yes	No

¹⁸ Under the FD&C Act, FDA must make a classification determination for the device that is the subject of the *de novo* within 120 days of the request [see section 513(f)(2)(A)(iii)]. For *de novo* requests submitted under the EAP program, FDA intends to make a determination in less than 120 days.

A. Criteria for Expedited Access Pathway Designation

For purposes of the EAP program, we based the criteria discussed below on the priority review criteria in section 515(d)(5) of the FD&C Act and discussed in the priority review guidance “[Priority Review of Premarket Submissions for Devices](#),” issued May 17, 2013.¹⁹ For purposes of this guidance, we are referring to the criteria as “EAP criteria.” Although priority review for devices was created to help expedite patient access to certain devices important to public health, FDA’s experience is that review times can take longer for these devices than for other devices reviewed under a PMA or *de novo* request because of the novel scientific issues these devices may raise. We believe that the EAP program may enable patients to have more timely access to these devices because of the earlier involvement of FDA during the device development process.

We provide below the criteria for the EAP Designation as well as examples of each criterion. The Agency believes that the examples provided would meet the EAP criteria. However, even if a device meets the EAP criteria, FDA retains sole discretion over whether to grant the device the EAP Designation based on benefit-risk factors or any other reason. When determining whether to grant an EAP Designation request, FDA intends to review the requests based on the EAP criteria, including the adequacy of the draft Data Development Plan submitted with the request, and relevant benefit-risk factors, including those discussed below.

To be eligible for EAP Designation, the following three criteria should be met.

1. The device is intended to treat or diagnose a life-threatening or irreversibly debilitating disease or condition.

Considerations include:

- *Whether the device is “intended” to treat or diagnose a life-threatening or irreversibly debilitating disease or condition:* In identifying devices that have an intended use to treat or diagnose a life-threatening or irreversibly debilitating disease or condition, including monitoring treatment for such a disease or condition, FDA intends to consider devices that are intended to have a positive effect on a serious aspect of the life-threatening or irreversibly debilitating disease or condition, such as an intended treatment effect on a serious manifestation or symptom of the disease or condition, improved diagnosis of such a disease or condition, improved quality of life, or other beneficial effects. FDA also intends to consider devices that have a specific intended use to cure, diagnose, mitigate, or prevent a life-threatening or irreversibly debilitating disease or condition in a population or subpopulation that meets the conditions for unmet medical need.
- *Whether a disease or condition is “life-threatening:”* FDA intends to consider a disease or condition life-threatening for purposes of the EAP program if it is a disease or condition for which the likelihood of death is high unless the course of the disease is

¹⁹ Available at: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089643.htm>.

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interrupted in a population or subpopulation that meets the conditions for unmet medical need. Examples of life-threatening diseases or conditions include but are not limited to: chronic or active hepatitis, myocardial infarction, cancer, and trauma.

- *Whether a disease or condition is “irreversibly debilitating:”* For purposes of the EAP program, FDA intends to consider 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 that meets the conditions for unmet medical need. 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 if severe enough).

2. The device meets at least one of the following criteria for addressing an unmet need:

- a. *No appropriate alternative treatment or means of diagnosis exists.*

For purposes of the EAP criteria, FDA generally considers an appropriate alternative to include a treatment, diagnostic, cure, mitigation, or preventative, including monitoring, treatment that:

- Is approved, cleared, or licensed by FDA in the U.S. for the same indication being considered for the device (whether a new device or an existing device for which a new indication is sought. In some cases, a treatment that is not approved, cleared or licensed for the indicated use or is not FDA-regulated may be considered an “appropriate alternative treatment” for purposes of the EAP criteria. For example, FDA may consider a therapy that is not approved, cleared or licensed by FDA to constitute an “appropriate alternative treatment” if the safety and effectiveness of the use is supported by compelling evidence, including evidence in published literature, and is considered the Standard of Care (SOC) in the U.S. FDA will consider on a case-by-case basis whether an approved EAP Device for which the confirmatory post-approval studies have not been completed is considered an “appropriate alternative treatment” for purposes of these criteria; and,
- Is relevant to current U.S. SOC for the indication.

There may be a substantial number of approved medical products with varying relevance in the current diagnosis and treatment of a life-threatening or irreversibly debilitating disease in the U.S., including devices that are no longer used or used rarely. FDA’s determination as to whether there is an

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approved alternative generally focuses only on treatment 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 or other experts for advice in assessing whether an approved therapy 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). FDA intends to determine what constitutes alternative treatment at the time of the request for EAP Designation, and at the time of approval of the pivotal clinical trial IDE, if a study is conducted in the US.

Examples include:

- An ablation catheter which offers the potential ability to treat atrial fibrillation. Catheters were approved for atrial flutter and there was no legally marketed ablation catheter indicated for the treatment of atrial fibrillation and, therefore, at the time of review, the ablation catheter met the criteria for “no approved alternative.”
- Continuous Glucose Monitoring (CGM) devices report glucose values continuously or at short intervals (i.e., every five minutes) for several days. They have built in alarms that can be programmed to alert the user if the results fall outside pre-set low and high thresholds. The first CGM intended to be used non-adjunctively to direct treatment decisions (i.e., replacing blood glucose testing) would qualify for the criterion “no approved alternative.”
- A first-of-a-kind Parkinson’s Disease testing device to differentiate symptoms from other diseases that may be less treatable.

Even where it is shown that no approved alternative treatment or means of diagnosis exists, the requirements for establishing a reasonable assurance of safety and effectiveness for the device must be met.

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- b. *The device represents a breakthrough technology that provides a clinically meaningful advantage over existing legally marketed technology.*

Breakthrough technologies have the potential to lead to a clinical improvement in the diagnosis, treatment, cure, mitigation, or prevention, including monitoring of treatment, of the life-threatening or irreversibly debilitating condition.

Examples 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, non-compressible wounds, not amenable to tourniquet application in the battlefield. This device offers immediate care for severe bleeding wounds in a battlefield setting until surgical care can be acquired, offering patients a potentially life-saving treatment when other methods of stopping severe bleeds are not an option.
- A genetic test capable of identifying DNA variants using blood from patients may be less sensitive than standard testing of surgically removed tumor, or bone marrow, but has the potential to offer patients a convenient, non-invasive sampling method.
- A fecal DNA test that provides information about whether the patient may have colon cancer, for which a negative result would likely mean forgoing an endoscopy.

- c. *The device offers significant, clinically meaningful advantages over existing legally marketed alternatives.*

The device has the potential to cure, provide a clinically important earlier or more accurate diagnosis or treatment monitoring, or offer important therapeutic or preventative advantages in safety and/or effectiveness over existing alternatives. FDA also intends to consider devices that offer important advantages in the mitigation of a life-threatening or irreversibly debilitating disease or condition. Such advantages may include superiority over current treatments for effects on serious outcomes (e.g., morbidity), substantially less risk than existing therapies, including the ability to provide a clinical benefit without the serious side effects associated with current treatments, addressing a known, important shortcoming of existing technology, and the ability to provide clinical benefit for those patients unable to tolerate current treatments.

Examples 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 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.

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- 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.
- d. *The availability of the device is in the best interest of patients (e.g., addresses an unmet medical need).*

That is, the device or new or expanded indication provides a specific public health benefit or addresses an unmet medical need of a well-defined patient population. For purposes of this guidance, an unmet medical need is a condition whose treatment or diagnosis is not addressed adequately by an available therapy or diagnostic. If no therapy or diagnostic exists for a life-threatening or irreversibly debilitating disease or condition, there is clearly an unmet medical need. When an available therapy or diagnostic exists, a new treatment or diagnostic would be considered to address an unmet medical need if it has an effect on a serious outcome of the disease or condition that is not known to be influenced by available therapy, or has a significantly improved effect on or diagnosis of a serious outcome(s) of the condition or disease compared to available therapy or diagnostic.

An example of a device, the availability of which is in the best interest of patients because it addresses an unmet medical need, could be a group of molecular tests to identify a large number of potential pathogens including common, rare, and/or emerging pathogens simultaneously. 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 meet the requirements for safety and effectiveness for the PMA. This guidance may allow greater flexibility for device developers to test new wide scope IVDs for both common and rare pathogens, resulting in devices with a broader diagnostic scope being brought to market. Also, this could allow for more rapid approval of modifications to these tests as new and emerging pathogens are discovered to allow them to be added 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 or whose disease has failed to respond to available therapy, or the treatment can be used effectively with other critical agents that cannot be combined with available therapy. This may also apply if the device provides effectiveness similar to available therapy, while:

- (1) avoiding serious harm that can occur with available therapy;
- (2) avoiding serious harm that causes discontinuation of treatment of a life-threatening or irreversibly debilitating disease or condition; or,
- (3) reducing the potential for harmful interactions with other therapies.

In addition, this may apply to a device that was designed or modified to address an unanticipated serious failure occurring in a critical component of an approved device for which there are no alternatives, or for which alternative treatment would entail substantial risk of morbidity for the patient. The device may also provide similar safety and

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effectiveness as available therapy or diagnostics, but with another intended benefit, such as improved patient compliance that is expected to lead to a reduction in serious adverse outcomes. Further, this may apply if the device addresses an emerging or anticipated public health need, such as a device shortage or public health emergency.

Examples include:

- 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 a therapeutic product may have severe toxicities and be detrimental to those who do not possess the variant without providing benefit. 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, see FDA’s guidance “[In Vitro Companion Diagnostic Devices](#),” issued August 6, 2014.²⁰
- An insulin pump that features a new mechanism to detect low blood glucose and automatically stop insulin delivery.

3. The sponsor submits an acceptable draft Data Development Plan.

For recommendations on the general information to be included in the draft Data Development Plan, please see [Attachment 2](#). The draft Data Development Plan should describe the clinical and nonclinical data that would be collected premarket and postmarket, the analysis plan for each, and, if applicable, the analytic method for combining the two. For PMA approval, the premarket data must be adequate to support a determination that there is reasonable assurance of safety and effectiveness. For a *de novo* request to be granted, data submitted must demonstrate that general controls or general and special controls support a classification of Class I or Class II, respectively.²¹ If a PMA sponsor proposes collecting certain data in the postmarket setting, rather than premarket, the draft Data Development Plan should provide the rationale for postmarket data collection and contain valid (clinical or nonclinical) scientific evidence to support the postmarket data collection, e.g., to support that the proposed surrogate endpoint is reasonably likely to predict clinical benefit. The draft Data Development Plan should also include a timeline for the development and marketing of the device as well as for the postmarket data collection.

Additional Considerations

Multiple devices for EAP designation with the same intended use are possible. Once an EAP designation is granted, other submissions for EAP designation may also receive EAP designation as they pursue approval until such time that safety and effectiveness with greater certainty have been demonstrated by any of the devices for which EAP designation was granted. FDA may

²⁰ FDA’s guidance “In Vitro Companion Diagnostic Devices” is available at <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf>.

²¹ More information about the *de novo* process is available at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080195.htm>.

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approve more than one EAP device for the same condition because of the possibility that the data from the post-approval study may not confirm certain safety or effectiveness aspects of the device under the conditions of use. However, when an EAP device has been found to be safe and effective based on premarket and post-approval data, no other devices with the same intended use will be designated as EAP, unless the criteria described in section III.A are met in light of the EAP device being on the market. For example, Device X was a breakthrough technology that provided a clinically meaningful advantage over existing legally marketed technology and was approved through EAP. Device Y has the same intended use as Device X and is a breakthrough technology that provides a clinically meaningful advantage over Device X. Therefore, even though Device Y has the same intended use as Device X, Device Y is eligible for EAP.

In cases where a sponsor has received EAP designation and another EAP device with the same intended use is approved or granted a *de novo* classification, FDA will not require a sponsor to modify their Data Development Plan. The standard for EAP designation will not change for a product as a result of FDA approving or granting *de novo* classification to another, similar product. FDA may consider devices as offering a “significant, clinically meaningful” advantage over existing approved alternatives, notwithstanding the availability of an EAP Device approved on the condition of a post-approval study.

The impact of device revisions depends on post-approval study findings and FDA would seek to address product revisions only in ways necessary to continue to provide a reasonable assurance of safety and effectiveness. As a general matter and in accordance with section 515(e)(1) of the FD&C Act and 21 CFR 814.46(a), FDA does not intend to withdraw a PMA for a valid EAP Device unless the data show the risks are greater than benefits, with appropriate mitigations (if any) taken into account, or the device was shown to be ineffective.

Revocation of EAP Designation

An EAP designation will not be revoked solely because a similar product is approved or a *de novo* request granted. FDA may revoke an EAP Designation at any time prior to approval upon written notice to the sponsor if FDA determines that:

- The information submitted in support of a request for EAP Designation, including, without limitation, the Pre-Sub package, or any related premarket submission contained an untrue statement of material fact or omitted material information, including false statements relating to data collection; or,
- Based on information available, the device is no longer eligible for an EAP Designation according to the EAP criteria outlined in this section of this guidance.

As a general matter, FDA does not intend to revoke EAP designation for other reasons.

B. Features of the Expedited Access Pathway

Under the Expedited Access Pathway, the Agency intends to proactively work with sponsors to try to reduce the time and cost from development to marketing decision, without changing FDA’s PMA approval standard of reasonable assurance of safety and effectiveness, the standards

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for granting *de novo* requests,²² or our standard of valid scientific evidence²³. The extent to which FDA can provide interactive review, senior management involvement, and a case manager, described below, will depend on resource availability. Features of the program include:

(1) Interactive Review

FDA intends to work with the sponsor to finalize a Data Development Plan prior to submission of the PMA or *de novo* request. 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. In addition, resources permitting and as appropriate, FDA intends to provide more extensive advice on efficient device development, interactive communications during device development, and greater interactive review of IDEs, PMAs, and *de novos*.

(2) Senior Management Involvement

FDA intends to involve, where appropriate and resources permitting, Office and Center-level senior management and experienced review staff in a proactive, collaborative, cross-disciplinary review.

(3) Case Manager

Where appropriate, and resources permitting, FDA may assign a cross-disciplinary case manager to facilitate efficient review of the Data Development Plan. The case manager coordinates activities between the review team and the sponsor, and, in consultation with the appropriate staff and management, considers the use of appropriate internal and external experts.

(4) Priority Review

FDA expects that the PMA for an EAP Device will receive priority review under 515(d)(5) of the FD&C Act. Under the FD&C Act, FDA must make a classification determination for a device that is the subject of a *de novo* within 120 days of the request [see section 513(f)(2)(A)(iii)]. For *de novo* requests submitted under the EAP program, FDA intends to make a determination in less than 120 days.

Given that the purpose of the EAP program is earlier access to devices that address an unmet medical need, FDA expects sponsors of devices under this program to, as appropriate, collect premarket and postmarket data, respond to FDA requests, and market their devices, if approved, in a timely manner. FDA intends to work interactively with sponsors through the EAP program to help ensure that these devices are developed and marketed in a timely manner in the U.S. Sponsors of these devices should give priority to resolving all scientific and regulatory issues during the review process.

²² See footnotes 2 and 16.

²³ See 21 CFR 860.7(c)(2)

C. Benefit-Risk Determinations for the Expedited Access Pathway for EAP Devices Subject to a PMA

FDA's Benefit-Risk Guidance explains the principal factors that FDA considers when making benefit-risk determinations in the premarket review of certain medical devices, including devices subject to PMAs. Two of the factors included in the Benefit-Risk Guidance that FDA may consider as part of making benefit-risk determinations are postmarket data collection and uncertainty.²⁴

Therefore, in accordance with the Benefit-Risk Guidance, as part of FDA's benefit-risk determination for EAP Devices subject to a PMA, FDA may consider the amount of data that may be collected in the postmarket setting, rather than premarket, and the level of acceptable uncertainty in the benefit-risk profile at the time of approval. In all FDA premarket approval decisions there is some degree 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 through significantly delayed availability of medical devices that 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 degree of uncertainty that FDA accepts at the time of approval depends on, among other factors, the probable benefits of the device.

As part of the benefit-risk determination for EAP Devices subject to a PMA, FDA may accept a greater degree of uncertainty of the benefit-risk profile for these devices if the uncertainty is sufficiently balanced by other factors, including the probable benefits for patients to have earlier access to EAP Devices (e.g., devices that treat a life-threatening disease when no alternative treatments are available), and adequate postmarket controls to support premarket approval. Generally, weighing the benefits against the risks for EAP Devices for which we would accept a greater degree 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.

To reduce the probable risk of harm to patients, FDA may consider the following information when assessing the benefit-risk factors provided in the Benefit-Risk Guidance. Although sponsors may not demonstrate each of the following to support that the device's probable benefits outweigh its probable risks, a demonstration of one or more of the following, particularly if it is quantifiable and explicit, can increase the likelihood of a favorable benefit-risk determination. As discussed in the Benefit-Risk Guidance, this information should be considered during the design, non-clinical testing, pre-IDE, and IDE phases as well as in assembling and assessing PMAs. In addition, this information should be considered in an EAP Designation request.

²⁴ See footnote 7.

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1. Premarket (clinical or non-clinical) data demonstrate that the probability of serious harm is low.
2. Postmarket patient exposure to the device prior to the required submission of postmarket data to FDA will be small.
3. The sponsor has a proven track record of a robust quality system.
4. A Data Monitoring Committee (also called Data and Safety Monitoring Board) will be used in the postmarket study to evaluate adverse events.
5. User training to help mitigate the probable risks of the device, which is described in the proposed labeling for the device.
6. The sponsor will provide patient labeling.
7. There is valid scientific evidence to demonstrate that the intended patient population is willing to tolerate the probable harm of the device in light of the level of uncertainty about the probable benefits and/or probable risks of the device.
8. There is a high likelihood that postmarket surveillance can quickly identify instances of serious patient harm.
9. There is a high likelihood that the required postmarket data collection will be completed in a timely manner.
10. The proposed postmarket data study is well-designed and feasible, taking into account the likelihood that patients will participate in the study once the device has been approved.

D. Types of Clinical Evidence That May Support Approval of EAP Devices Subject to a PMA

Because of the potential benefit to public health from devices that meet the criteria for EAP Designation, approval of the PMA may be based on the types of clinical evidence described below. Although a sponsor may use these types of clinical evidence in support of a PMA submission for an EAP Device, it is neither a criterion for the EAP program nor is it a comprehensive list of the types of clinical evidence that may be used to support approval of EAP Devices.

Study endpoints should prespecify the minimum clinically meaningful effect. For surrogate outcomes, modeling could be used to define the minimum clinically meaningful effect. For composite outcomes, the rationale for the composite and clinically meaningful effect size should be explicit. The effect of each component outcome should be also evaluated for clinical significance.

(1) Intermediate and Surrogate Endpoints

As discussed above, EAP Devices must meet the statutory standard of PMA approval of reasonable assurance of safety and effectiveness. FDA may, as a basis for PMA approval, rely on assessments of a device's effect on an intermediate or surrogate endpoint that is reasonably likely

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to predict clinical benefit (on the condition that remaining uncertainty about the predictive relationship between a surrogate and clinical benefit is minimized through confirmatory post-approval studies or on the condition that clinical benefit is verified through confirmatory post-approval studies).

A PMA for an EAP Device that relies on a surrogate endpoint should include or reference evidence that it is reasonably likely to predict clinical benefit of the device. However, if a CDRH-qualified Medical Device Development Tool (MDDT)²⁵ is used consistent with its qualified context for use, the sponsor generally does not need to provide additional evidence in the PMA to support the use of the surrogate endpoint, though confirmatory postmarket studies may still be required. Because FDA would generally accept a greater level of uncertainty about the likelihood that an intermediate or surrogate endpoint predicts the intended clinical benefit for EAP devices than for other PMA devices (and, therefore, accepting a greater level of uncertainty about the benefits of the EAP device), as discussed below, FDA would generally require postmarket confirmatory data as a condition of approval.

Clinical study endpoints²⁶ selected to assess clinical benefit²⁷ as a basis for regulatory approval can be conceptualized in a spectrum. At one end of the spectrum are the clearest clinical endpoints of a disease itself, such as irreversible morbidity or mortality. Closely related endpoints are events that affect a patient's health status, ability to function, or quality of life (intermediate endpoints). In the middle are endpoints that are defined, in part, on both clinical signs or symptoms and biomarkers ("composite endpoint"). At the other end of the spectrum are endpoints defined entirely by biomarkers or other such measurements, with a less direct relationship to patient experience.²⁸

The following sections outline general considerations related to intermediate and surrogate endpoint use as the basis for approval for EAP Devices.

Optimal Use of Intermediate or Surrogate Endpoints

Use of intermediate or surrogate endpoints may allow for smaller trials or shorter follow-up, or be easier to measure than traditional clinical outcomes of a disease or condition. Optimal conditions for using intermediate or surrogate endpoints include when the traditional endpoint is a rarely occurring event or delayed in its presentation (as in certain chronic diseases); when measurement of the endpoint is invasive, uncomfortable, costly, or easily confounded; or when the treatment effect is small, and therefore would require trials of impractical size in order to

²⁵ For more information about MDDTs, see FDA's website at <http://www.fda.gov/MedicalDevices/ScienceandResearch/MedicalDeviceDevelopmentToolsMDDT/>.

²⁶ For purposes of this guidance, a clinical study endpoint is a detected symptom or measurement of a function, or any clinical characteristic or variable that reflects how a patient feels (e.g., symptom relief), functions (e.g., improved mobility), or survives, measured at a specific time point.

²⁷ For purposes of this guidance, a clinical benefit is a positive therapeutic or diagnostic effect that is clinically meaningful in the context of a given disease or condition. The clinical benefit should be weighed against a treatment or diagnostic risk to determine whether there is an overall benefit for patients (i.e., a favorable benefit-risk profile).

²⁸ See, generally, IOM (Institute of Medicine). 2010. *Evaluation of biomarkers and surrogate endpoints in chronic disease*. Washington, DC: The National Academies Press.

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meet statistical significance. For example, trials of percutaneous coronary interventions, such as stenting, traditionally included myocardial infarction (MI) as a clinical study endpoint. As advances in medicine and clinical care of MI have substantially improved patient outcomes, the required sample size to demonstrate improvements in or equivalent incidence of MI is now correspondingly larger. By incorporating evidence such as the clinically driven need for a repeat procedure as part of a composite endpoint, the number of clinical events is larger, which allowed FDA to accept smaller, more efficient trials than would be required with traditional endpoints. Confirmatory postmarket data were required to provide better precision around safety in terms of MI rates for stents approved using such endpoints.

Intermediate Endpoints

For purposes of this guidance, an intermediate endpoint is used in a clinical study as a measurement of clinical benefit or risk concerning a symptom or measure of function that is not the ultimate outcome of the disease (e.g., exercise tolerance in trials of device treatments for heart failure). An intermediate endpoint may also be a clinical study endpoint measured at an earlier time than has historically been accepted (“intermediate temporal endpoint”).²⁹ Intermediate endpoints are not uncommon in premarket trials for medical devices.

Examples of Intermediate Endpoints:

- Exercise tolerance and symptoms, together with evidence of no adverse effect on survival.
- Heart failure hospitalization rate, together with evidence of no adverse effect on survival.
- Symptoms of hyperglycemia.
- Angina frequency.
- Findings from non-IVD devices, such as Doppler, ultrasound, or digital mammography.

The availability and appropriateness of the intermediate endpoints depend on the device and its intended use.

Improvement according to an intermediate endpoint is generally of value to patients even if this does not lead to reduced morbidity or mortality, and could be considered as a basis for marketing approval by FDA. Incorporating an intermediate endpoint into premarket clinical trials is most often useful in settings in which the disease course is long and an extended period of time is required to measure the clinical benefit of a device, such as long-term use devices used in a chronic disease setting.

Surrogate Endpoints

For purposes of this guidance, a surrogate endpoint is not itself a measure of clinical benefit, but is used in trials as a substitute which is reasonably likely to predict clinical benefit, based on

²⁹ Use of intermediate temporal endpoints (e.g., earlier assessment of osteoarthritis progression-free, based on symptoms and patient function, at 12 months instead of at 24 months) is particularly useful with some adaptive design studies.

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epidemiologic, therapeutic, pathophysiologic or other scientific evidence. The types of measurements which may be used as a surrogate endpoint are *in vitro* laboratory or medical imaging measurements, or physical signs (e.g., blood pressure measurements in trials of antihypertensive therapeutics, as a surrogate for clinical endpoints such as stroke, myocardial infarction, or mortality).

Measurements which could be considered as potential surrogate endpoints may focus on assessment of:³⁰

- The underlying cause of the disease (e.g., elevated uric acid and gout, low thyroxin levels and hypothyroidism).
- The state of the pathophysiologic pathway leading to the clinical outcome (e.g., left ventricular hypertrophy and congestive heart failure).

Whether a Surrogate Endpoint is Reasonably Likely to Predict Clinical Benefit

A PMA that relies on surrogate endpoints should include or reference evidence that the endpoint is reasonably likely to predict the clinical benefit of a device.³¹ This section provides an overview of some of the important factors to consider in identifying and assessing the predictive potential of surrogate endpoints. However, this section does not address clinical evidence requirements, because they are not readily generalizable.

Predictive Relationship Between Surrogate Endpoints and Clinical Benefit

Whether a surrogate endpoint is reasonably likely to predict clinical benefit is a function of the scientific plausibility of the relationship between the disease, endpoint, and the expected device effect, and the empirical evidence to support that relationship. The empirical evidence may include epidemiological, pathophysiological, therapeutic, or other scientific evidence. When considering evidence of a predictive relationship between the endpoint and clinical benefit, it is important to do so in the context of the nature of the disease as well as the mechanism of action of the device.

Use of a surrogate endpoint depends on the quality of data and strength of evidence supporting the measure, and on the context in which it is applied (“context of use”).³² When there is strong evidence demonstrating a predictive relationship between a measure and clinical benefit, it may be accepted for use as a “well-established” surrogate endpoint in a clinical study which will serve as the basis for approval. A measure which is reasonably likely to predict clinical benefit could be used as a basis for regulatory approval in some instances such as for an EAP Device

³⁰ Note the examples in this section are provided for illustrative purposes, and FDA will determine acceptability of a surrogate endpoint on a case-by-case basis. Submissions under the EAP program that rely on a surrogate endpoint should include evidence to support the use of a surrogate endpoint.

³¹ Data produced by a surrogate endpoint will ultimately be interpreted in context of the severity, rarity or prevalence of the condition and availability or lack of alternative treatments. Refer to the MDDT draft guidance for additional information. See footnote 25.

³² See footnote 25.

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intended for a life-threatening or irreversibly debilitating disease or condition with no alternatives, and considered for broader use in multiple device development programs once qualified through the MDDT process. When there is weak or inconsistent evidence to support a predictive relationship between a measure and clinical benefit, the measure is not suitable for use to support approval of a PMA marketing application for an EAP Device. The principal risk of accepting surrogate endpoints as the basis for approval is the possibility that patients will be exposed to a device that may ultimately be shown to have an unfavorable benefit-risk profile.

If a surrogate endpoint has failed to predict clinical benefit in a properly designed trial, or in the same disease or a related disease, it weighs against reliance on the endpoint as a basis for approval. A demonstration of one or more of the following can increase the likelihood that a surrogate endpoint will be accepted to support the PMA approval of an EAP Device:

- There is a clear biologically plausible predictive relationship to a clinical benefit, in the context of the nature of disease and mechanism of action of the device, because:
 - The causal pathway is well understood;
 - The disease pathway is not complex; and/or,
 - The surrogate is not remote from the clinical benefit on the biological pathway of the disease or condition.
- The measurement validity itself is well established.
- The epidemiologic, therapeutic, pathophysiologic or other scientific evidence to support the predictive relationship between the surrogate and clinical benefit is extensive, reliable and consistent (e.g., the effect on the surrogate has been shown to predict clinical benefit in similar devices in a similar disease context).
- The relationship between the surrogate endpoint and clinical benefit is defined (the more precise the relationship, the stronger the basis for concluding that an effect on the surrogate endpoint would have a reasonably likely effect on clinical benefit).
- The product is intended for short-term use, such that treatment may be halted if unintended adverse effects arise.

Examples of Surrogate Endpoints:

- Lowering blood pressure (as measured by sphygmomanometry) is not a direct measure of clinical benefit but elevated blood pressure has been shown in numerous long-term outcome studies of antihypertensive drugs to be reasonably likely to predict stroke and mortality, and is widely established as an underlying cause of stroke, heart failure, renal failure, and accelerated coronary artery disease. Blood pressure has been accepted as a surrogate endpoint in regulatory trials of antihypertensive drugs, and could be considered as a surrogate endpoint in trials of antihypertensive devices, provided there is sufficient evidence of a known or reasonably likely predictive relationship with clinical benefit, considering the mechanism of action of the device.
- Cytomegalovirus (CMV) viral load as evidenced by a laboratory measure of CMV DNA in plasma is not a direct measure of clinical benefit but has been shown to be reasonably likely to predict morbidity and mortality associated with CMV disease in transplant

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patients. Prolonged suppression of viral load is known to reliably predict an effect on survival. CMV viral load could serve as a surrogate endpoint for device trials, provided there is sufficient evidence of a known or reasonably likely predictive relationship with clinical benefit such as survival.

- Early pathophysiologic analysis of biopsied breast lesions is not a direct measure of clinical benefit but has been shown to be reasonably likely to predict morbidity and mortality associated with breast cancer. Pathophysiological analysis of biopsied breast lesions could serve as a surrogate endpoint for device trials, provided there is sufficient evidence of a known or reasonably likely predictive relationship with clinical benefit such as survival.
- Already marketed established diagnostics, such as HbA1c, can be used as surrogate endpoints for many diabetes devices.

Conditions of Approval for EAP Devices Approved Based on Intermediate or Surrogate Endpoints

As described previously, clinical study endpoints selected to assess clinical benefit as a basis for regulatory approval can be conceptualized in a spectrum, with clear clinical endpoints of a disease such as irreversible morbidity or mortality at one end of the spectrum and surrogate endpoints at the other end. FDA would generally require postmarket confirmatory data as a condition of approval when surrogate or intermediate endpoints are used as a basis for approval for EAP Devices.

Postmarket considerations when relying on an intermediate or surrogate endpoint as the basis for approval of EAP Devices:

- If an intermediate endpoint is used for the basis of approval, continue the premarket study into the postmarket phase to obtain more long-term data or to gain additional precision around an important endpoint (see the “Two-Phase Studies” section below).
- If uncertainty remains regarding the predictive relationship between the surrogate endpoint and clinical benefit, a postmarket study should primarily address clinical outcomes of the specific disease to confirm the anticipated clinical benefit and the overall benefit-risk profile of the device. It is possible to design a study which also generates additional evidence of the predictive relationship between the surrogate endpoint and clinical benefit, which could be utilized to further establish use of the surrogate for other purposes.

(2) Two-Phase Studies

We may consider approval based upon premarket study results (premarket phase) that meet a pre-specified criterion such as a pre-defined predictive probability of success, or a pre-specified significance level. The remaining confirmatory information would then be obtained from postmarket data (postmarket phase). Both premarket and postmarket phases should be carefully planned in advance and described in the protocol. The design of the premarket study should

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always ensure that the probability of statistical Type I error at the premarket phase is controlled at a level agreed upon by FDA and the sponsor at the design stage. The agreed upon degree of uncertainty will determine the criterion for premarket phase success and will depend on factors such as:

- The amount of benefit expected to be provided by the EAP device; if the benefit is very large, more uncertainty could be tolerated at the first stage in order to expedite the time to market.
- The amount of risk to untreated patients posed by delaying approval.
- The amount of prior information that can be leveraged from experts, science, engineering, nonclinical tests, and similar devices at the planning phase.
- The timeframe necessary to test device durability or survival. Waiting for a prolonged study of device durability or survival may not be feasible or justified when compared with the risk of delaying treatment to patients.

The results of the premarket phase could be based on a smaller sample (fewer subjects), less time of device use, or a combination of both. For example, if FDA would otherwise require a study with 200 subjects followed for 2 years, FDA may approve the device after receiving promising results from 100 subjects who use the device for 6 months, provided there is reasonable assurance the 6-month data predicts the 2-year outcomes. If so, approval of the device may be conditioned on the sponsor providing the remaining data at the completion of the study – i.e., the data from 200 subjects using the device for 2 years. Some of these subjects may have been recruited during the first phase of the study, prior to approval, but have not completed their follow-up at the time of approval. Some subjects may also be recruited after completion of the premarket phase.

Diagnostics with a public health impact can address unmet medical needs for both individual patients through early diagnosis, as well as informing the public health response by providing more detailed, timely information on disease incidence. These types of diagnostic assays can provide information on timing of infections (e.g., whether infection occurred within the last 6 months or less recently). Individuals in the early stage of infection are often at highest risk of transmission, and treatment and contact tracing can be effective in lowering risk. However, in the past significant barriers existed for properly evaluating the performance of these tests in clinical cohorts. By allowing post-market data collection to better confirm these tests' medical benefits, uncertainties in the timing of infection can be validated while significantly streamlining the review process for devices with such a public health or surveillance design scope.

- *Example:* Migration is an approach used for approval of Class III IVD devices when a previously approved, licensed, or cleared assay is migrated to another system for which FDA has not evaluated assay performance. The paradigm is suitable in cases when sufficient knowledge can be derived for the documentation of design controls, risk analyses, and prior performance studies on an already marketed system. This paradigm uses smaller and more focused analytical and clinical data sets, along with prior knowledge of device design and performance. For more information, see *Assay Migration Studies for In Vitro Diagnostic Devices: Guidance for Industry and FDA Staff*, available at

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<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm092752.pdf>.

(3) In Vitro Diagnostics

For in vitro diagnostic devices (IVDs), clinical validity is often evaluated with clinical performance measures that quantify how well the diagnostic device output agrees with a subject's true status.³³ That is, how well it identifies, quantifies, detects or predicts an event or target condition as determined by a clinical reference standard. The choice of appropriate clinical performance measures depends on the intended use of the device, the nature of the diagnostic device output and the clinical reference standard.

In the absence of a new prospective clinical study, FDA may in some cases accept alternative experimental designs unique to diagnostics to generate evidence demonstrating the analytical and clinical validity of an IVD for premarket approval. Some examples are listed below, and versions of these may be acceptable to support approval of an EAP device. To better appreciate the level of evidence of experimental designs unique to diagnostics demonstrating analytical and clinical validity of an IVD for premarket approval, additional IVD examples can be obtained by searching the PMA database at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm>.

- Banked samples from previously performed prospective studies can be analyzed with an investigational IVD to demonstrate clinical validity when the samples represent the intended use population for the IVD, the samples are demonstrated to be stable for the analyte(s) being detected (i.e., identical performance in stored as compared to fresh samples), the current standard of care for the condition or disease state is applicable to the sample collection and study period, and clinical results (including longitudinal follow-up when necessary) relevant to the IVD's proposed intended use are available for the samples. If this pathway is chosen, a prospective statistical analysis plan should be in place prior to beginning the analysis.
- In cases where the clinical validity of a biomarker test may be fully established in the literature, only analytical data that demonstrate a genetic test can accurately detect the variant may be necessary.
- For tests for rare diseases or conditions with established clinical validity (i.e., via the published literature) and for which it is extremely difficult or unethical to obtain clinical samples for analytical validation, it may be possible to use contrived samples. Samples may be contrived by mixing a virus, pathogen, or analyte with a clinical matrix (e.g., whole blood or stool) provided that comparability to clinical specimens can be justified. In the case of extremely rare mutations, a postmarket clinical investigation may not be feasible. The sponsor should propose a path – possibly literature-based – to support approval. The sponsor should be prepared to discuss their approach during the Pre-Sub process.

³³ FDA does not require data on clinical utility to be submitted.

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Sponsors may consider utilizing the above strategies for the premarket component of an EAP Device. For instance, when an IVD meets the EAP criteria, but it is challenging to comprehensively complete analytical and/or clinical evaluations for approval, an initial evidence base (including use of banked specimens from previous studies, use of relevant studies in the literature, use of contrived specimens to supplement testing of clinical samples including representative analytes) may be acceptable for approval of the device if it provides a reasonable assurance of safety and effectiveness, through a reasonable benefit-risk conclusion, adequate analytical testing is provided, and a feasible, well-designed, and scientifically sound post-approval study for confirming clinical performance is proposed. Some scenarios that serve as examples are listed below:

- An initial study of banked samples from a clinical trial may support clinically meaningful performance between marker-positive and marker-negative patients with a confidence level appropriate to support premarket approval for a device intended for an unmet medical need. A post-approval study to better define performance would then require the collection and testing of additional samples from appropriate ongoing studies, or the design and conduct of a new prospective study.
- A genetic test for both common and uncommon variants could be a candidate for the Expedited Access PMA if, for example, common variants are supported by robust, prospective clinical evaluation and uncommon variants are supported by initial clinical data with clinical justification for the expected performance range (e.g., confidence interval of positive predictive value). The post-approval study should collect additional data on the uncommon variants to provide greater clarity with respect to analytical and clinical performance.
- New IVDs that can reliably identify rare conditions, such as viral central nervous system infections, meet a significant unmet medical need. At this time, diagnosing these infections can be challenging and complex. Patients must often be treated empirically if infection is suspected, as the prognosis for untreated infection is quite poor. It is currently challenging to bring such tests to market, due in large part to the difficulty in obtaining large enough sample populations to properly test the clinical validity of the devices. The criteria for expedited access could enable companies developing devices to more feasibly evaluate their clinical validity. This would increase the availability of safe and effective devices for clinical use.

It should be noted that in some situations FDA may require a bridging study to evaluate the potential impact of various changes (e.g., specimen processing or storage, device or software modifications) on analytical and clinical performance. The kinds of information that can be collected postmarket will depend on the IVD, its intended use, and other factors. Therefore, further details, including when and how bridging studies may be conducted, depend on the device. The sponsor should be prepared to discuss their approach during the Pre-Sub process.

Types of evidence that might support PMA approval of other diagnostics under the EAP program will depend on the device. Examples include:

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- A nanocamera with nano-light source that is injected into the blood stream and transmits images, for example, of the interior surfaces or plaque to more accurately support diagnosis of arterial disease.
- A new imaging device that identifies malignant breast cancer with very high accuracy that could reduce both mortality from breast cancer and unnecessary tests or treatments.

Companion Diagnostic Considerations

An IVD companion diagnostic device is an *in vitro* diagnostic device that provides information that is essential for the safe and effective use of a corresponding therapeutic product. It should be noted that certain, but not all, companion diagnostics, when appropriate, and with consultation from CDER or CBER, may be considered for the Expedited Access PMA pathway. CDRH will not automatically grant EAP designation for companion diagnostics for which the therapeutic component is undergoing expedited development and review (i.e., Orphan Designation, Fast Track, Accelerated Approval, Priority Review, and/or Breakthrough Therapy). Eligibility for EAP is determined on a case-by-case basis.

Although CDRH, CDER, and CBER will collaborate on a product review to streamline the process and reduce burdens on sponsors, sponsors are responsible for coordinating their submissions to FDA so the review timelines for a companion diagnostic are aligned with those of the corresponding therapeutic. Companion diagnostics will be considered for EAP designation when the sponsor requests EAP designation via the Pre-Sub process (see Attachment 1 for details about the process). Sponsors should discuss the need for concurrent review of different components of a companion diagnostic during the Pre-Sub process.

The types of evidence that might support PMA approval of companion diagnostics under the Expedited Access PMA would include intermediate and surrogate endpoints as well as clinical endpoints. The specifics will depend on the product and the study proposals provided by the sponsor. For example, if a drug is reviewed via the accelerated drug approval pathway based on a surrogate endpoint, the companion diagnostic may be considered for the EAP pathway. Because the safety and efficacy of a companion diagnostic is linked to that of the therapeutic product, the surrogate endpoint for the IVD will be that determined to be acceptable for the therapeutic product. This surrogate endpoint will be determined using processes already established by CDER or CBER. However, CDRH encourages early discussion of surrogate endpoints in the context of the request for EAP designation during the Pre-Sub process. Because safety and effectiveness for a companion diagnostic depends on the therapeutic product, failure of the therapeutic component in confirmatory studies will result in revocation of EAP status for the companion diagnostic unless the device otherwise meets the criteria in this guidance.

In some situations (e.g. a test that combines multiple analytes into a score), a reference method may not exist for direct analytical comparison. In these instances, alternative approaches to address analytical performance may be appropriate. These considerations may be discussed in the Pre-Sub requesting EAP Designation (see [Attachment 1](#) for more discussion on the EAP Designation process).

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(4) Sources of Clinical Evidence

Sources of clinical evidence may include prospective clinical studies or retrospective data related to use of the device, such as data collected in a registry or OUS data applicable to the U.S. population. In all circumstances, information should be valid scientific evidence as defined in 21 CFR 860.7(c)(2).

E. Manufacturing Considerations for EAP Devices Subject to a PMA

On a case-by-case basis, FDA may, at its discretion, allow a sponsor to provide less manufacturing information in their PMA for an EAP Device, for example, when the sponsor has a good track record for quality systems compliance and there are not new, unique manufacturing issues that could adversely impact product quality or performance. Note, a device must be in conformance with the Quality System (QS) regulation (QSReg) and the sponsor must submit adequate information in the PMA to meet the requirements under section 515(c)(1)(C) of the FD&C Act and 21 CFR 814.20(b)(4)(v). As with other PMAs, sponsors of an EAP device should submit in their PMA information described in the FDA guidance entitled, “[Quality System Information for Certain Premarket Application Reviews](#),” issued on February 3, 2003.³⁴

In appropriate cases, FDA may also at its discretion, forgo inspection of certain manufacturing sites as part of the premarket review of EAP Devices and instead conduct those inspections after product approval. 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:

1. Finished device manufacturing sites with no prior inspectional history or inspectional history that is 5 or more years old, measured from the filing date of the application, would be inspected before approval of the EAP Device.
2. Finished device manufacturing sites that have been inspected in less than 2 years from 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 this PMA, may be inspected after approval of the EAP Device.
3. Finished device manufacturing sites that have been inspected within 2 to 5 years from the filing date of the application, for which the inspectional outcome was No Action Indicated or Voluntary Action Indicated and for which the inspectional coverage is relevant to this PMA, may be inspected after the EAP Device is approved if, in addition to submitting all other information required in a PMA under section 515(c) of the FD&C Act and 21 CFR 814.20, the sponsor submits the following:

³⁴ Available at:
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070897.htm>.

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- A declaration stating that all activities at the site comply with the Quality System Regulation (21 CFR part 820); and,
- Information demonstrating that, as part of design validation [21 CFR 820.30(g)], 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 appropriate levels; for example, using standards such as ISO 14971:2007, "Medical devices – Application of risk management to medical devices."

Where an inspection is not conducted prior to approval of the PMA for an EAP Device, FDA intends to conduct an inspection within 12 months after approval. In appropriate circumstances, FDA may consider an inspection that is classified as Official Action Indicated³⁵ and that was not brought into QSRReg conformance within a reasonable time after receipt of written notice, to be a grounds for PMA withdrawal under section 515(e)(1)(E) of the FD&C Act.

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 QSRReg decision from FDA. It should be noted that this applies to PMA sponsors that are manufacturing their own device or sponsors who intend to have another entity manufacture their device for commercial distribution in the U.S. We generally would then approve the product once we had adequate assurances of compliance regarding the applicable quality systems of the manufacturer(s).

F. Conditions of Approval for EAP Devices Subject to a PMA

To facilitate earlier patient access to devices that demonstrate the potential to address an unmet medical need, the approval of an EAP Device subject to a PMA may involve accepting a higher degree of uncertainty about the benefit-risk profile of the device at the time of approval by collecting certain data in the postmarket setting rather than premarket, while still ensuring that the statutory standard for premarket approval of reasonable assurance of safety and effectiveness is met. Therefore, FDA may impose postmarket requirements as part of the EAP program, including conditioning the approval of EAP Devices subject to a PMA on continuing evaluation and periodic reporting on the safety, effectiveness, and reliability of these devices for their intended uses, in accordance with 21 CFR 814.82(a)(2). These postmarket data will enable the Agency to assess the risks and benefits of these devices with a higher degree of certainty and, when necessary to protect patient safety, take appropriate postmarket action as described in section III.G below.

FDA may also impose conditions of approval on the labeling of EAP Devices under 21 CFR 814.82(a)(3) if important for the device's safe and effective use (e.g., in order to ensure that patients and healthcare providers have complete and accurate information regarding what is

³⁵ For a discussion on inspections that may be classified as Official Action Indicated, see page 33 of the FDA Compliance Program Guidance Manual (7382.845), available at <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM244277.pdf>.

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known about the benefits and risks of the device). In addition, if necessary to provide for a reasonable assurance of the safety and effectiveness of these devices, FDA may restrict the sale, distribution, or use of the device as a condition of approval under 21 CFR 814.82(a)(1).

(1) Post-Approval Studies

In circumstances where post-approval data collection is appropriate, FDA may require this as a condition of approval. These studies may include both clinical and non-clinical testing. The kind of information that can be relegated to a post-approval study depends on the device and its intended use. FDA intends for the design and timeline of the post-approval studies to be part of the Data Development Plan. In addition, the approval order will specify the agreed upon timeframe for the sponsor to complete the post-approval study, conduct analyses and submit the data to FDA. In appropriate instances, FDA may order the sponsor to conduct postmarket surveillance under section 522 of the FD&C Act in lieu of a post-approval study.³⁶ Examples of a post-approval study under 21 CFR 814.82 include:

- A post-approval study for a test for anti-tumor drug resistance provided information on how the test results applied clinically, provided added assurance of safety and effectiveness for its intended use to further assess in vitro tumor resistance compared to in vivo response or lack of response, and provided support for device reliability validating the controls and cut-off. The information resulted in the removal of limitations in the labeling.
- Post-approval studies for a test to determine if surgical tumor margin removal is successful prior to closing a patient address the time to obtain a clinically useful result relative to real life surgical experience.
- A post-approval study was conducted to assess clinical effectiveness of a reagent change to support bench testing evidence that the change in formulation had no impact on test results.

If a post-approval study is required, generally it should begin within 6 months of the approval date, if not sooner, and the study should be completed, analyzed, and submitted to FDA within 3 years of the approval date, if not sooner. FDA and the sponsor will consider these timeframes when designing a post-approval study during development of the Data Development Plan.

(2) Reporting Requirements for Post-Approval Studies

FDA may impose periodic reporting on the safety, effectiveness, and reliability of the device for its intended use under 21 CFR 814.82(a)(2) (e.g., periodic reporting of the status and interim data or analyses of the required postmarket data collection). The reports required to be submitted will be included in the post-approval order. For more information, see “Guidance for Industry and FDA Staff: Procedures for Handling Post-Approval Studies Imposed by PMA Order,” available at

³⁶ The failure or refusal of a manufacturer to comply with section 522 is a prohibited act under section 301(q)(1)(C) of the FD&C Act, 21 U.S.C. 331(q)(1)(C). Further, under section 502(t)(3) of the act, 21 U.S.C. 352(t)(3), a device is misbranded if there is a failure or refusal to comply with any requirement under section 522 of the FD&C Act. Please note that violations of section 301(q)(1)(C) or 502(t)(3) may lead to enforcement action including seizure, injunction, prosecution, and/or civil money penalties.

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<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071013.pdf>.

(3) Labeling

FDA may impose certain labeling requirements as a condition to PMA approval, under 21 CFR 814.82(a)(3) that are important for the device's safe and effective use (e.g., information on the risks and benefits of the use of the device). Any labeling requirements will be included in the approval order. In general, certain labeling issues specific to the EAP process should be considered: (1) at the time FDA grants approval of an indication; (2) after the successful completion of post-approval studies upon which approval was conditioned; or (3) if FDA withdraws approval of one or more indications granted under approval for an EAP Device whose labeling includes other approved indications.

If data is collected postmarket rather than premarket, the labeling of a device approved through the Expedited Access Pathway program should include a succinct description of the uncertainty about anticipated benefits and risks and the extent of data that supported approval and the required post-approval study or studies. For example, if there is uncertainty regarding an anticipated clinical benefit because a surrogate endpoint that was reasonably likely, but not validated, to predict clinical benefit was used to support approval, this should be explained in the labeling, along with a description of the clinical benefit that has not been fully established and a brief description of the post-approval study or studies. If the device was approved with more uncertainty than typically expected, the labeling should describe the uncertainty concerning the benefits and risks of the device and clearly state that it is greater than what is typically expected. The labeling should include language similar to the following: "For more information about the conditions required to approve this device, see FDA's website at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm>."

The device labeling should clearly define the indication(s) for use, including the specific patient population(s) studied (e.g., Device X was studied for the treatment of Y disease in Z population) and state the patient populations that will be studied in the post-approval context.

(4) Use of Registries

In some cases, it may be appropriate to use data from a registry to meet the requirements of the condition of approval study. Availability of registry data may help determine the safety and effectiveness of the device, or to verify records, reports, or information submitted to the agency [21 CFR 814.82(a)].

G. Postmarket Actions for EAP Devices Subject to a PMA

There are several actions that the sponsor or FDA may, as appropriate, take in the postmarket setting as a result of the required conditions of approval, depending on whether the sponsor conducts and completes the required post-approval study, and submits, in a timely manner, the data from the study to FDA as specified in the approval order, as well as on the study's results. FDA may take enforcement action if the sponsor has not met the required conditions of approval,

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including failure to initiate or complete a post-approval study specified in the approval order for the device.

In addition, as provided in the FDA guidance entitled, “[Procedures for Handling Post-Approval Studies Imposed by PMA Order](#),” issued June 15, 2009 (“post-approval guidance”),³⁷ FDA posts certain information about the post-approval studies for devices on FDA’s website at: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/PMA_pas.cfm. FDA intends to post this information for EAP Devices under a separate section on FDA’s website for devices approved under the Expedited Access PMA program in order to provide increased transparency to the public regarding the status of the postmarket data collection for EAP Devices in accordance with applicable confidentiality rules and policies. The information will include the purpose of the study, the timeframe for study completion, conducting analyses, and submission to FDA, and the status of the study.

These actions that the sponsor or FDA may take in the postmarket setting include, but are not limited to, the following:

(1) Submission of a PMA Supplement

The results from the post-approval study may trigger the need for the sponsor to submit a PMA supplement to FDA in accordance with 21 CFR 814.39(a) if the sponsor makes a change affecting the safety or effectiveness of the device. Examples include, but are not limited to, narrowing or expanding the indication for use of the device, labeling changes, and changes in the performance or design specifications.

Labeling Changes

Depending on the results of the post-approval study, the sponsor could revise the device’s labeling, with the approval of FDA, to reflect the population and condition for which a clinical benefit was directly established in the post-approval study or studies, including expanding the indication for use, narrowing the indication for use, or removing or revising language in the labeling regarding the level of uncertainty about the approved indication for use. The sponsor may decide to revise other sections of labeling (e.g., contraindications, warnings, precautions, adverse events and clinical studies), with FDA’s approval, to ensure that, based on the new data, the labeling adequately describes the safety and effectiveness of the device.

Importantly, information learned about a device postmarket can change the information required in device labeling. For example, new information about an adverse event may require labeling changes to device instructions for use or to warnings or precautions to ensure the device complies with section 502(f) of the FD&C Act and 21 CFR Parts 801 and 809, as applicable. During its review of post-approval study reports, FDA may discuss with the sponsor changes to the labeling based on the study findings to ensure the device labeling has adequate directions for use.

(2) Safety Communications

³⁷ Available at <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070974.htm>.

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In some instances, it may be in the best interest of public health for FDA to issue a safety communication, such as if the post-approval study raises new safety concerns, but FDA believes there is still a reasonable assurance of safety and effectiveness. More information about safety communications is available on FDA's website here:

<http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/default.htm>.

(3) Panel Meeting

As described in the post-approval guidance, FDA may seek the advice of panels when considering the progress of, or data from the post-approval study, such as when the results of the study may be difficult to interpret.³⁸

(4) Administrative and Enforcement Actions

As discussed above, getting the right balance between premarket and postmarket data collection – specifically, where appropriate, a greater reliance on postmarket collection – can reduce the extent of premarket data submission and directly impact when patients will have access to high-quality, safe and effective medical devices. However, greater reliance on postmarket data collection could undermine patient safety if the necessary and timely data collection does not occur.

To protect patient safety, FDA may take a variety of actions if the Agency concludes that based on the data from the required post-approval study or other source there is a lack of reasonable assurance that the device is safe or effective under the conditions of use, or if the sponsor has not met the required conditions of approval under 21 CFR 814.82, including failure to initiate or complete a post-approval study specified in the approval order. For example, failure to comply with certain post-approval requirements under 21 CFR 814.82(a)(2) may cause the device to be misbranded under section 502(t)(2) of the FD&C Act and constitute a prohibited act under section 301(q)(1)(B) of the FD&C Act, which could result in seizure, injunction, and/or civil money penalties. Failure to comply with a post-approval requirement under 21 CFR 814.82(a)(3) may cause the device to be misbranded under section 502 of the FD&C Act.

FDA recognizes that the agreed on timeframe in the approval order to complete the post-approval study, conduct analyses and submit the data to the Agency is a best estimate and that circumstances may arise outside of the sponsor's control that may adversely affect the ability of the sponsor to complete the post-approval study on time. Therefore, when appropriate, FDA intends to be reasonably flexible about the timeframe for completing a post-approval study and submitting data to the Agency. Timeframes are discussed in section F (1) of this document. The sponsor should communicate all anticipated delays to FDA.

In accordance with section 515(e) of the FD&C Act and 21 CFR 814.46, FDA may also withdraw PMA approval of an EAP Device if, for example:

- On the basis of the data from the required post-approval study or studies, or other new information with respect to such device, evaluated together with the evidence available to

³⁸ See footnote 37.

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FDA when the PMA was approved, FDA finds that there is a lack of a showing of reasonable assurance that the device is safe or effective under the conditions of use prescribed, recommended or suggested in the labeling;

- The sponsor fails to meet any post-approval requirement imposed by the PMA approval order, which includes failure to complete a post-approval requirement within the timeframe established in the approval order; or
- On the basis of new information, evaluated together with the evidence available to FDA when the PMA was approved, FDA finds that the labeling, based on a fair evaluation of all material facts, is false or misleading in any particular, and such labeling is not corrected within a reasonable time after receipt of written notice from FDA.

If FDA determines there are grounds for withdrawal, the Agency may ask the sponsor if they would like to voluntarily request withdrawal of approval under 21 CFR 814.37(d). If the sponsor does not voluntarily request the Agency to withdraw approval, FDA will notify the sponsor of FDA's proposal to withdraw approval via a notice of opportunity for an informal hearing under 21 CFR Part 16.³⁹ If the sponsor does not request a hearing or if after the Part 16 hearing FDA decides to proceed with the withdrawal, FDA will issue the sponsor an order withdrawing approval of the application.⁴⁰ The order will be issued under 21 CFR 814.17, will state each ground for withdrawing approval, and will include a notice of an opportunity for administrative review under section 515(e)(2) of the FD&C Act. FDA will give the public notice of an order withdrawing approval of a PMA, in accordance with 21 CFR 814.46(e).

H. Program Evaluation

Beginning 1 year from the effective date of this guidance and annually thereafter for the next 3 years, FDA intends to evaluate the EAP program and make available to the public a report including:

- The number of EAP designation requests FDA received that year;
- The number of EAP designation requests FDA granted that year;
- The number of PMAs approved that year that were designated as EAP;
- The number of *de novo* requests granted that year that were designated as EAP;
- The number of EAP devices for which postmarket studies are ongoing that year;
- For every completed postmarket study that year, a description of the results of the study; and,
- For every device approved under EAP, the number of serious adverse events reported for that device, as well as whether the device was withdrawn or recalled.

At the end of this time period, if not sooner, FDA intends to determine whether any changes should be made to the EAP program.

³⁹ 21 CFR 814.46(c)

⁴⁰ 21 CFR 814.46(d)

Attachment 1

Expedited Access Pathway Process

I. When to Request EAP Designation

Sponsors developing a device that may qualify for the EAP Designation and would like to be considered for the program should submit a Pre-Sub, as described in FDA’s [Pre-Sub Guidance](#).⁴¹ The EAP criteria factors described earlier in this guidance should be apparent during the early stages of development. Therefore, in most cases, a sponsor should submit a Pre-Sub for an EAP Designation prior to commencement of an IDE pivotal study. Consideration for the EAP program is not required and is entirely voluntary on the part of the sponsor. If FDA determines that a device may be eligible for this program, and the sponsor has not yet submitted a Pre-Sub requesting EAP Designation, FDA intends to inform the sponsor of the program.

If sponsors are interested in this program, FDA strongly recommends early interaction with FDA on planned nonclinical and clinical studies in order for FDA to provide the sponsor with early feedback on their draft Data Development Plan.

II. Content of a Request for EAP Designation

A sponsor intending to pursue EAP designation should submit a Pre-Sub containing the information recommended to be included in a Pre-Sub package as described in the Pre-Sub Guidance. In addition, FDA recommends that the sponsor include the following information in their Pre-Sub package:

- 1) A discussion of why the device meets the EAP criteria described in section III.C of this guidance, including any relevant supporting documentation.
- 2) A draft Data Development Plan that describes the premarket and postmarket data collection and the explanation and justification for the proposed balance of premarket and postmarket data collection. In addition, the sponsor should provide a timeline for the development and marketing of the device, and for the postmarket data collection. For recommendations on the general information to be included in the draft Data Development Plan, please see [Attachment 2](#).

⁴¹ For more information on the Pre-Sub Program, see FDA’s guidance “Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff” (<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf>).

II. FDA Response

A. EAP Designation

FDA intends to review the Pre-Sub within 30 days of receipt to determine whether or not to grant EAP designation, based on the EAP criteria described in this guidance and relevant benefit-risk factors, including those discussed in this guidance. FDA intends to notify the sponsor of its determination in writing within 30 days of receipt. If there is insufficient information for FDA to make a decision about EAP designation, FDA may request the sponsor submit additional information. If FDA requests additional information from the sponsor, FDA will notify the sponsor in writing whether or not EAP designation is granted within 30 days of the date of the request for additional information. If FDA has not received enough information in time to make a decision by 30 days after a request for additional information is sent, FDA intends to deny the EAP designation. If the sponsor submits additional information, it should be as a supplement to their Pre-Sub.

Granting the EAP designation does not mean FDA agrees with the sponsor's draft Data Development Plan at the time the designation is granted. Although FDA may agree with the general concepts outlined in a draft Data Development Plan at the time of EAP designation, FDA intends for the sponsor and FDA to work together to continue to develop the plan prior to submission of a PMA or *de novo* request. FDA's granting of the EAP designation does not imply any determination that any data or proposed study design included in the Pre-Sub will support future marketing approval.

The notification of EAP designation should be signed by the appropriate Office Director or their designee. If FDA grants the EAP designation, FDA intends to include the following information in the written notification:

- Confirmation that FDA intends to work closely with the sponsor to provide guidance on the Data Development Plan for the device;
- Notice that the sponsor should ensure the device continues to meet the criteria for EAP designation; and,
- A point of contact for the review of the device.

The sponsor should include the Pre-Sub number and the date of the FDA correspondence granting EAP designation in the cover letter accompanying the IDE application, *de novo* request, or PMA. Even if a device does not qualify for the EAP Designation, the sponsor may utilize the Pre-Sub review process, as described in the Pre-Sub guidance, to request feedback from FDA on their plan to use postmarket controls to reduce the extent of premarket data collection for a device subject to a PMA.

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Sponsors who disagree with FDA's decision not to grant EAP designation should consult FDA's guidance titled "Center for Devices and Radiological Health Appeals Processes."⁴² Because Expedited Access Pathway devices are intended for unmet medical needs for life threatening or irreversibly debilitating diseases or conditions, the appeal may follow the telescoped review process in which a dispute is elevated to the Center Director.

B. Review of PMA or *De Novo* Request

The sponsor and FDA should agree on the final Data Development Plan prior to submission of the PMA or *de novo* request. In addition, as discussed in section III.F of this guidance, FDA intends to impose certain postmarket requirements in the PMA approval order.⁴³ The approval of the PMA or granting of a *de novo* classification for the EAP Device will be signed by the appropriate Office Director or their designee.

C. Review of Postmarket Data Collection for EAP Devices Subject to a PMA

Sponsors should generally follow the procedures discussed in post-approval guidance, unless otherwise indicated below.

Submission of Post-Approval Study Protocol

As discussed in the post-approval guidance, FDA recommends that the proposed post-approval study protocol be submitted in the PMA submission. This protocol should also be part of the Data Development Plan. Although the post-approval guidance indicates that in certain instances a PMA may be approved without an agreed upon post-approval protocol, FDA generally does not intend to approve an EAP Device without an agreed upon post-approval study protocol.

Submission and Evaluation of Interim and Final Post-Approval Study Report

Completion of the required post-approval study should occur within the timeframe specified in the approval order. This should generally occur no later than three years after PMA approval, but may vary depending on the device type and the type of post-approval study. The timeframes for completing the study, conducting analyses and submitting data to FDA will be specified in the PMA approval order.

In rare cases, FDA may extend the post-approval study timeframe if progress has been made but, in spite of good faith efforts by the sponsor, unforeseen circumstances have led to a modest delay in completion of the study. In certain cases, FDA may also extend the timeframe if a supplement for a modification to the device is submitted to FDA reasonably soon after approval of the PMA. When submitting a supplement for a modification, the sponsor should provide an assessment of the impact of the modifications to the ongoing post-approval study. FDA evaluates this assessment as part of the review of the supplement.

⁴² Available at

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm284651.htm>.

⁴³ 21 CFR 814.82

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The sponsor should follow the procedure in the post-approval guidance for submitting the interim and final post-approval study status reports, as well as for the recommended content and format for these reports. The appropriate frequency for the submission of interim reports will be specified by FDA in the PMA approval order. In addition, submission of the final post-approval study report should occur within the timeframe included in the approval order. Generally, a sponsor should submit the required final post-approval study report no later than three months after completion (at the point of data lock) of the post-approval study, as defined as the completion of the clinical study report. However, if the sponsor has an appropriate basis for needing additional time beyond three months, FDA may, at its discretion, grant an extension for an amount of time agreed upon by the Agency and the sponsor.

Labeling changes

As discussed in section III.G.1 of this guidance, depending on the results of the post-approval study or studies, the labeling for the EAP Device should be modified as a result of the successful completion of the post-approval study or studies. A PMA supplement must be submitted for any labeling change that meets the criteria in 21 CFR 814.39.

Attachment 2

Draft Data Development Plan

As discussed in Attachment 1 of this guidance, sponsors developing a device that may qualify for the Expedited Access Pathway and would like to be considered for the program should submit a Pre-Sub. Sponsors should include in the Pre-Sub, among other information, a discussion of why the device meets the EAP criteria described in section III.A of this guidance, including any relevant supporting documentation, and a proposed draft Data Development Plan. The draft Data Development Plan should include three sections:

- (1) An explanation and justification for the proposed balance of premarket and postmarket data collection, if a premarket-postmarket data shift is proposed and applicable;
- (2) A description and summary of the data collection plan, including study synopses and study design; and,
- (3) A timeline for the development and marketing of the device as well as for the postmarket data collection.

The proposed data collection plan should specify all data the sponsor intends to collect premarket and postmarket (if applicable) to support the EAP designation, approval of the PMA or granting of a *de novo* classification, and confirmatory evidence supporting approval (if applicable). FDA expects that the draft Data Development Plan will evolve during premarket development and review and that the sponsor and FDA will ultimately agree upon the Data Development Plan prior to submission of a PMA or *de novo* request.

FDA recognizes that the sponsor may not have all the information listed below at the time of EAP Designation request. FDA's feedback on the draft Data Development Plan represents our best advice in accordance with the information provided and known at the time of review. FDA intends that feedback will not change, provided the information submitted in a future IDE or marketing application is consistent with what was provided in the Data Development Plan and that the data in future submissions do not raise important new issues that affect safety or effectiveness.

Furthermore, FDA may not grant an EAP Designation if insufficient detail is provided in the draft Data Development Plan. Therefore, it is in the best interest of the sponsor to provide FDA with a comprehensive draft Data Development Plan to facilitate FDA's review. Interested sponsors may request a pre-submission meeting to discuss the type of valid scientific evidence that will be necessary to demonstrate that the device is safe and effective for its intended use. [For more information, consult the Pre-Sub Guidance and "Early Collaboration Meetings Under the FDA Modernization Act (FDAMA)."]

I. Explanation and Justification for Proposed Balance of Premarket and Postmarket Data Collection for EAP Devices Subject to a PMA

FDA recommends that the sponsor provides a detailed explanation of the extent of data that the sponsor plans to collect premarket and postmarket and a description of the type of data that the sponsor intends to include in the PMA (e.g., use of surrogate endpoints). Include an explanation of how data will be analyzed premarket and postmarket. In addition, FDA recommends that the sponsor provide a justification for how the proposed data collection plan may yield sufficient valid scientific evidence for FDA to determine at the time of approval of the premarket application that there is a showing of reasonable assurance of safety and effectiveness for the device. Finally, to assist FDA in its review, FDA recommends that the sponsor incorporate a discussion of the relevant benefit-risk information (described in section III.C of this guidance) as part of the justification.

II. Data Collection Plan

Generally, the following elements should be included in the data collection plan. FDA recommends that the sponsor provide an outline of nonclinical and clinical testing either planned or already completed, and clearly indicate which data the sponsor intends to collect premarket and which data, if any, the sponsor intends to collect postmarket (if applicable). Please note that information provided elsewhere in the Pre-Sub or previously submitted by the sponsor to FDA in other submissions may be incorporated by reference. As discussed above, FDA understands that the sponsor may not have all the following information available at the time that they are requesting EAP Designation.

- Device Description. A device description, including a description of the principles of operation of the device (including components) and properties relevant to the clinical function.
- Proposed Labeling. The major elements of the proposed labeling, including the proposed intended use/indications for use, contraindications, warnings, precautions, and instructions for use. FDA understands that labeling proposed at these early stages may be drafts; however, the sponsor should provide sufficient information to convey the conditions of and instructions for use of the device.
- Nonclinical Studies. A summary, study design and protocol, as available, for each of the proposed or completed nonclinical laboratory studies that the sponsor intends to submit to FDA to support the future PMA submission or *de novo* request. These studies may include (as applicable):
 - Sterilization
 - Biological/Microbiological
 - Immunological
 - Toxicological/Biocompatibility
 - Chemistry/Analytical (for IVDs)
 - Shelf life
 - *In vivo* animal modeling

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- Bench testing – mechanical and electrical testing
- Clinical Studies. Note that in some instances, there may be only one planned clinical study (e.g., if a sponsor is conducting staged studies). However, in other cases the sponsor may be conducting more than one clinical study. For example, a sponsor may be conducting a study with a surrogate endpoint prior to PMA approval, and a confirmatory study post-approval. For each proposed (or completed) clinical study, you should provide the following information:
 - purpose of study
 - study objectives and hypotheses
 - study design
 - study population (including subject inclusion and exclusion criteria and definitions and source of comparator group)
 - sample size calculation (statistically justified and based on study hypothesis)
 - primary and secondary endpoints (including definitions for study endpoints, success criteria, list of expected adverse events/complications, standard operating procedures for a determination of relatedness with the device and/or the procedure)
 - length of follow-up, follow-up schedule, description of baseline and follow-up assessments
 - description of data collection procedures (including recruitment plans, enrollment targets, plans to minimize losses to follow-up, follow-up rate targets, quality assurance, and control)
 - planned statistical analyses
 - data collection elements, and draft informed consent forms, and, if applicable, IRB approval forms
 - proposed reporting requirements
 - study milestones/timeline elements, including:
 - expected date of study initiation
 - expected monthly number of study sites with IRB approvals
 - expected date of initiation of subject enrollment
 - expected number of subjects enrolled per month
 - expected date for subject enrollment completion
 - expected date to complete follow-up of all study participants
 - if applicable, information related to intermediate milestones (e.g., evaluation of surrogate endpoints in a study that also measures clinical benefits)
 - Potential regions where subjects will be included

III. Timeline

Include a timeline for the development and marketing of the device as well as for the postmarket data collection.