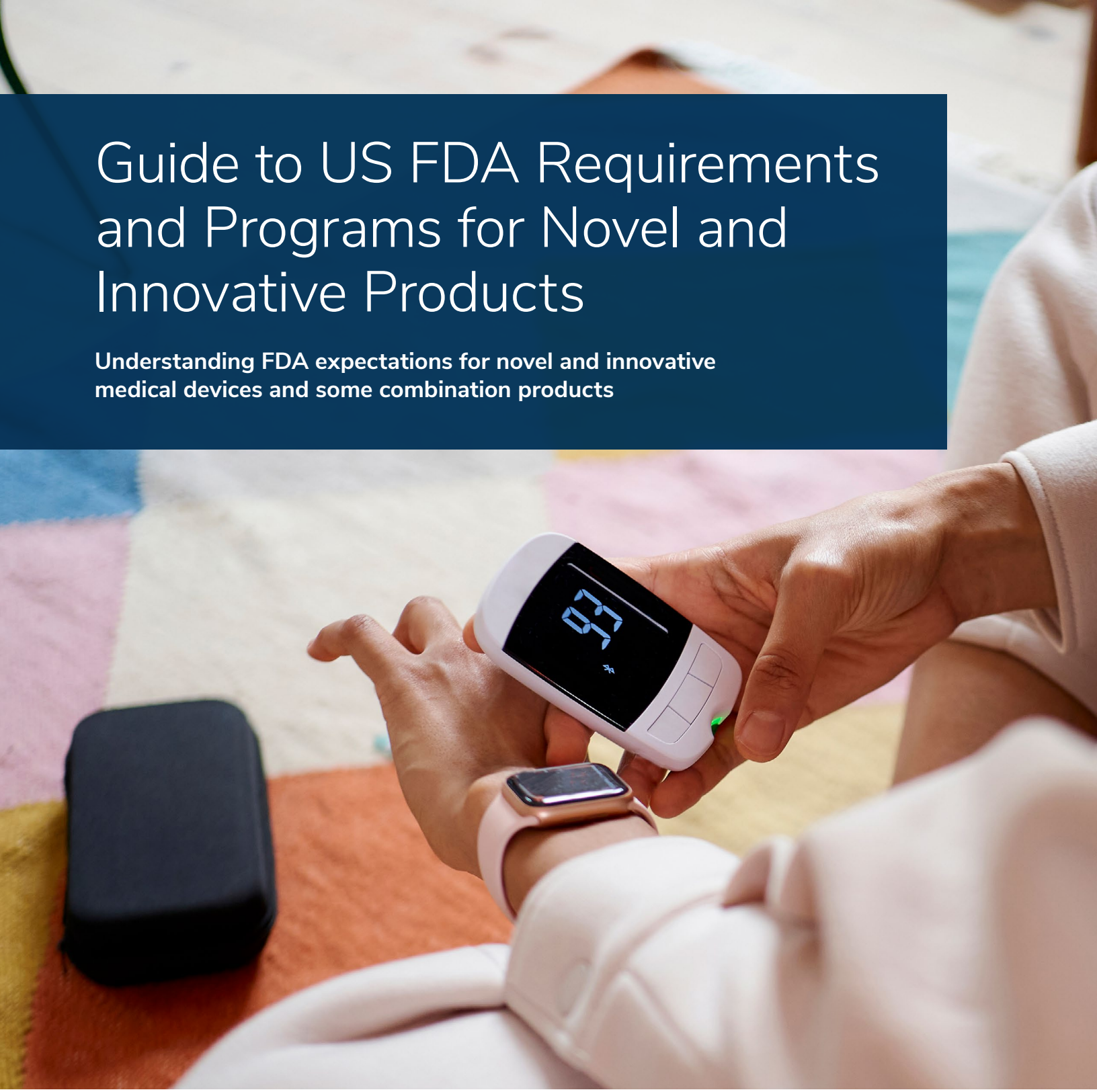
Guide to US FDA Requirements and Programs for Novel and Innovative Products

Understanding FDA expectations for novel and innovative medical devices and some combination products



Sarah Marie Fitzgerald, RAC
Senior Consultant
sarah.fitzgerald@ul.com

EMERGO
by UL

November 2023

Advancing technologies, common framework

Advances in technology continue to change the landscape of the medical field. With advances in areas such as 3D printing, nanomaterials, augmented and virtual reality, and artificial intelligence/machine learning (AI/ML), the range of novel and innovative medical devices and combination products is continuing to grow rapidly. The challenge for both industry and the US Food and Drug Administration (FDA), is to determine within the existing regulatory framework the best way to bring these new products to healthcare providers and patients as soon as possible while ensuring safety and effectiveness.

The FDA's medical device classification system is based on an array of agency-assigned product codes tied to the intended use, technological characteristics, risk and type of controls required to provide reasonable assurance of adequate safety and effectiveness for the intended use of a device. Title 21 of the **Code of Federal Regulations (21 CFR)**[1] provides the definition, device classification and regulatory requirements for each product code. Individual product codes are also tied to a specific pathway to market. A **combination product** is a product that includes two or more types of medical products (medical device, drug and/or biologic) and is reviewed through the FDA center determined to be most relevant based on the product's primary mode of action (PMOA).[2] Throughout this paper, "medical device" is used and applies to combination products with a medical device PMOA.

The three most common pathways in which to place a medical device onto the US market are summarized below:

- **No pre-market evaluation by the FDA –** This applies to most Class I and some Class II devices where the FDA has determined that the device is submission-exempt. Additionally, devices under enforcement discretion fall into this submission type. For Class I (generally considered low-risk) devices, Good Manufacturing Practice, Establishment Registration with Device Listing and post-market controls are deemed sufficient. Class II (moderate-risk) devices also must follow special controls.
- **Pre-market notification (510(k))**[3] **–** This applies to most Class II and some Class I and Class III (high-risk and novel) devices. These are generally devices that are not life-supporting or life-sustaining. The device must be shown to be substantially equivalent to an existing device with the same intended use and technology sufficiently similar that there are no new questions related to safety or effectiveness.
- **Pre-market approval application (PMA)**[4] **–** This applies to most Class III devices, including most that are life-supporting or life-sustaining. These devices must undergo specific evaluation related to effectiveness, meaning that clinical evaluation is generally required before they can enter the market.

Truly novel devices that do not fit into existing regulations or product codes are automatically deemed Class III devices, even if the risk may not be high.

Is the device novel?

Not every innovative device is truly novel from a regulatory perspective. To be novel, either the intended use is different from existing devices or the fundamental scientific technology is different enough that there are new or different questions related to safety or effectiveness. It is generally easier to get devices to market that are not novel. For example, a device that provides improvements to a device's accuracy or performance may be innovative, but if it has the same intended use and a sufficiently similar fundamental scientific technology, then it may not be novel from a regulatory standpoint.

However, if a device manufacturer develops a device that does not adequately fit the description (intended use and/or fundamental scientific technology) of an existing FDA product code, it is a novel device from a regulatory standpoint. This can include employing an existing device in a new intended use, an innovative design or a unique principle of operation.

What to do if your device is truly novel

Do not panic! The FDA has programs in place and has published guidance documents (links provided in references section at the end), to assist the medical device industry in understanding and aligning with the FDA on expectations.

Furthermore, the FDA has recognized the importance of novel devices and has developed programs to encourage manufacturers to bring such devices to market as part of its strategic priorities.[4]

The following outlines the potential options through which a company may choose to engage the FDA to confirm whether a device is innovative or novel, with descriptions as to the appropriateness and expectations of each.

Confirm that the device is novel

The first thing to do is to confirm that the FDA will consider the device novel. There are three main ways to do this, depending on the specific situation. The first two are for devices where there does not appear to be an appropriate regulation and/or product code: A 513(g) or request for information can be submitted to the FDA if the product is a medical device, or a request for designation (RFD) can be submitted if the device is a combination product (mixed or for use with a specific drug and/or biologic). The third way to confirm whether a medical device is novel applies to cases where there appears to be an appropriate product code but there are questions concerning whether there is an appropriate predicate device on the market. In such a case, the manufacturer would submit a Pre-Submission Q-Submission (Pre-Sub) to the FDA.

If a device's intended use and/or technological characteristics are not clearly described by an existing product code or regulation, a medical device manufacturer may be left to wonder what the classification is for their innovative device and how to get it onto the U.S. market.

For potentially novel devices, the manufacturer may want to consult with the FDA to determine the regulatory pathway and basic expectations prior to significant development to ensure that appropriate resources can be devoted to the product.

Request for information (513(g)) — FD&C Act Section 513(g)[5]
For medical devices, if a manufacturer is unsure whether an existing product code appropriately fits their device's intended use and technology, they can submit a request for information to the FDA soliciting their opinion. This submission is often simply called a 513(g).

A 513(g) request addresses questions related to the classification of a medical device (or a determination that the product is not a medical device) and basic submission requirements applicable to a device. The FDA intends to respond within 60 days of receiving a written request and will generally provide the following information to the requestor:

- The agency's assessment, based on the information submitted in the request, of the generic type of device — e.g., classification regulation — or whether the product is not a medical device
- The device class and product code (generic type of device)
- Whether a premarket approval (PMA), 510(k) or neither is required to market devices of the particular class within that generic type or whether the device is a candidate for a De Novo classification request to enter the market
- Other basic requirements applicable to devices of the particular class within that generic type
- Whether a guidance document has been issued regarding the generic device type including the exercise of enforcement discretion
- Whether additional FDA requirements may apply, such as periodic reporting applicable to radiation-emitting products

The FDA is clear that its response to a 513(g) request for information is non-binding and is only a response based on information provided by the requestor. However, the FDA intends to honor it unless there are differences in understanding of the device in subsequent interactions. Once a device manufacturer has the FDA's opinion on the device's classification, product code and applicable market pathway, they can approach the FDA again to clarify specific requirements such as test plans, as discussed further below for a Pre-Submission Q-Submission. It is recommended that manufacturers provide their assessment and opinion on the appropriate classification and pathway to market.

Request for designation (RFD) — FD&C Act Section 563[6]
For combination products, which are products that include a medical device and a drug and/or biologic, it may be necessary to request that the FDA designate the agency Center with authority over the product based on the device's PMOA through an RFD to the Office of Combination Products (OCP).

The FDA will review the intended use, principles of operation, mechanism of achieving its intended purpose, materials and other relevant information to render a decision regarding the product's PMOA. If the product acts on the body primarily in a structural or physical manner in accordance with the FDA's definition of a medical device,[7] the product will be designated a device under the primary jurisdiction of the Center for Devices and Radiological Health (CDRH). Combination products also undergo review by the Center with jurisdiction over any secondary mode(s) of action. It is critical to provide sufficient scientific evidence and justification to support a specific mode of action in these submissions to obtain the correct designation.

The FDA will provide a letter of designation with their response, which is a binding decision. The outcome of the designation will determine not only the FDA Center(s) that will review the product, but the type of application (device, drug, biologic) required. It is possible to submit a 513(g) after an RFD in certain cases.

Pre-Submission Q-Submission (Pre-Sub)[8]
A Pre-Submission Q-Submission, or Pre-Sub, provides a mechanism for a sponsor to obtain the FDA's feedback prior to a premarket submission like a 510(k) or PMA. Pre-Sub questions should pertain to the planned device and submission and provide sufficient information to allow the FDA to respond appropriately to the questions posed. Questions on sufficient testing are very common. Emergo by UL recommends a Pre-Sub prior to conducting any animal (other than biocompatibility) or clinical testing to align with the FDA on expectations. A novel device from a regulatory standpoint nearly always requires one of these sorts of tests.

A Pre-Sub should not be used to determine the classification of a device. If a manufacturer believes that a specific classification and product code are appropriate for their device but there are enough differences in its indications for use, design, principle of operation or other technological characteristics compared to existing devices such that there is uncertainty about using an identified predicate or similar device, a Pre-Sub may be used to support alignment with the FDA.

Feedback from a Pre-Sub is non-binding, but the FDA intends to honor it unless there are differences in understanding of the device or in specific knowledge related to safety or effectiveness in subsequent interactions.

A Pre-Sub is not used to provide a classification determination but can be used when there are questions about how the device compares to devices on the market, especially from a substantial equivalency standpoint (for a 510(k) submission). Before submitting a marketing submission for an innovative or novel medical device, a Pre-Sub is nearly always highly recommended to support alignment with the FDA.

Special marketing submissions for novel devices

Understanding the regulatory submission required
In addition to the three most common pathways briefly summarized above (PMA, 510(k) or pre-market submission-exempt), you might have other less common but just as valid pathways to market. These potential pathways are De Novo classification request, humanitarian device exemption and emergency use authorization, which are summarized below.

De Novo classification request (De Novo)[9] — FD&C Act Section 513(f)(1) and 513(f)(2)
If a novel device is not currently covered by an existing product code and/or there is no appropriate predicate device for substantial equivalence determination, it will by default be considered a Class III device (automatic Class III designation, per 513(f)(1)), regardless of its risk level. A Class III device generally requires a PMA submission. However, if the device is less than high-risk, a De Novo classification request is an appropriate submission type. Additionally, a De Novo should include the manufacturer's proposed classification, rationale and, if the classification is to be Class II, the proposed special controls for the device.

Humanitarian device exemption (HDE)[10] — FD&C Act Section 520(m)
A humanitarian device exemption (HDE) is a special pathway for high-risk devices intended for the treatment or diagnosis of diseases or conditions that affect or are manifested in fewer than 8,000 individuals in the United States per year, i.e., for a rare disease or condition. Whereas most high-risk devices need to demonstrate both safety and effectiveness through a clinical trial, these devices are granted an exemption from the effectiveness requirements of section 514 and 515 of the Act and can be approved for marketing via an HDE. Note that a clinical trial is likely still required, but it is intended to address safety and probable benefit, and therefore is likely to be much smaller.

First, a device must be designated as a humanitarian use device (HUD) through a special application intended to demonstrate that the device meets the criteria of being intended for a rare disease or condition, as described above.

If the FDA designates a device as a HUD, the manufacturer may submit an HDE submission for marketing authorization. Along with an adequate risk assessment and verification and validation testing to determine whether the probable benefits outweigh the risks, there must be a discussion on why there is no comparable device available to treat or diagnose the condition. In other words, for a specific indications for use, there can only be one HDE.

Note that in most cases, devices authorized under this pathway may not be sold for a profit but rather only to cover the costs of research, development and manufacturing, with limited exceptions. Special reporting requirements also apply. Because of this, very few original HDEs are sought. From 2012 to 2022, only 24 original HDEs were authorized.

Emergency use authorization (EUA)[11] — FD&C Act Section 564
An emergency use authorization (EUA) is a pathway for devices intended to be used in an emergency to diagnose, treat or prevent serious or life-threatening diseases or conditions where certain criteria are met, including that there are no adequate, approved or sufficiently available alternatives. Although these are of special importance during a pandemic, they may also be used when there are no other alternatives legally available for conditions that the FDA could constitute an emergency. In 2023, for example, not only was EUA a valid pathway for certain devices related to COVID-19, but also for those related to mpox (monkeypox), anthrax, Ebola, H7N9 influenza, Middle East respiratory syndrome coronavirus (MERS-CoV), nerve agents and the Zika virus.

Requirements for EUAs are highly variable depending on the threat level of the disease or condition and what is available to help with the situation. For example, if there is no alternative, the requirements may be relatively low. If there are alternatives, but they are not sufficiently available, requirements may be higher. For COVID-19, specific guidance was provided for different types of devices that might be used during the pandemic and what the FDA currently expected. In other cases, a Pre-Sub is advised.

It is important to note that most marketing authorization submission types do not expire if the manufacturer continues to meet standard requirements such as annual establishment registration. EUAs are intended to be temporary and may be revoked at any time with or without advance notice.

Investigational device exemption (IDE)[12]
An investigational device exemption (IDE) is not a marketing authorization submission, but rather a submission required prior to beginning certain clinical trials. Essentially, it is an exemption from standard requirements that do not allow an unauthorized device to be shipped or used so that the devices can be researched in a clinical trial.

As a summary, prior to beginning a clinical trial, IDE requirements must be considered. Some noninvasive trials or trials intended for purposes other than to obtain safety and effectiveness data for a marketing submission are exempt. For trials that present only non-significant risk, an abbreviated IDE where all requirements are met but the FDA does not need to approve an application prior to trial initiation is sufficient. For trials that present significant risk, an IDE application must be submitted and approved by the FDA prior to initiation of the trial.

Remember: Before starting any clinical trial, you need to ensure that all requirements are met to protect patients. This includes understanding the type of investigational device exemption (IDE) required or if the trial is exempt. An IDE for a significant-risk device trial requires FDA approval prior to initiation.

Expediting market entry for novel devices

Special programs for novel medical devices
To expeditiously bring a novel device to market, the FDA has implemented special programs intended to provide clear expectations and prioritize review. These programs include the Breakthrough Device (BTD) Program, the Safer Technologies Program (STeP) and the early payor feedback program.

Breakthrough Device (BTD)[13] Program and Safer Technologies Program (STeP)[14]
In 2015, the FDA introduced a new program for novel medical devices to provide an expedited pathway to market called the Expedited Access Pathway for Unmet Medical Needs for Life-Threatening or Irreversibly Debilitating Diseases or Conditions, or EAP for short. In 2018, this was replaced by the Breakthrough Device (BTD) Program, and in 2021 the Safer Technologies Program (STeP) was introduced. BTD and STeP are very similar programs, the main difference being which devices qualify. In both cases, the requirements can be summarized as they must be devices that require a marketing submission (like a PMA, De Novo, or 510(k)) and that offer a significant advantage over devices currently in the market. BTD is intended for devices that address life-threatening or irreversibly debilitating diseases or conditions, while STeP is for devices intended to address less serious diseases or conditions.

Manufacturers can request either designation through a special Q-Submission.

If the appropriate designation is granted, the sponsor has access to additional special Q-Submissions to interact in a more timely and interactive way with the FDA and engage with senior FDA staff. These special Q-Submissions include a data development plan (DDP), which provides an outline of expected data collection requirements over the entire life cycle, and a clinical protocol agreement (CPA), which aligns on clinical trial design. DDPs can be helpful for BTD and STeP devices; careful consideration of the appropriate balance of pre-market and post-market data collection is expected, and some data may be allowed to be collected post-market instead of pre-market. This Q-Submission can confirm those expectations. CPAs are, unlike other Q-Submissions, considered binding and provide more certainty for the sponsor. These are especially helpful as clinical trial design is usually critical to ensuring the safety and effectiveness of novel devices.

Supporting alignment with the FDA is critical to obtaining marketing authorization. The Q-Submission program is intended to allow this before submitting a marketing authorization and is highly recommended for novel devices.

Additionally, the marketing submission will be prioritized for review. These designations are not themselves marketing authorizations, so the appropriate submission must still be made.

Although there is no guarantee, it is our understanding that insurance providers consider these designations in determining reimbursement and, at least in some cases, offer higher reimbursement for designated devices.

As of March 31, 2023, 794 devices had been granted BTD (or the predecessor designation under the EAP) and 67 had been granted marketing authorization. Approximately 70% of devices that request a BTD designation receive one. At the **end of 2022**,[15] 14 devices had been granted STeP and none had yet been granted marketing authorization. The FDA noted that there had been 30 requests for this program, indicating approximately a 47% chance of being included in the program.

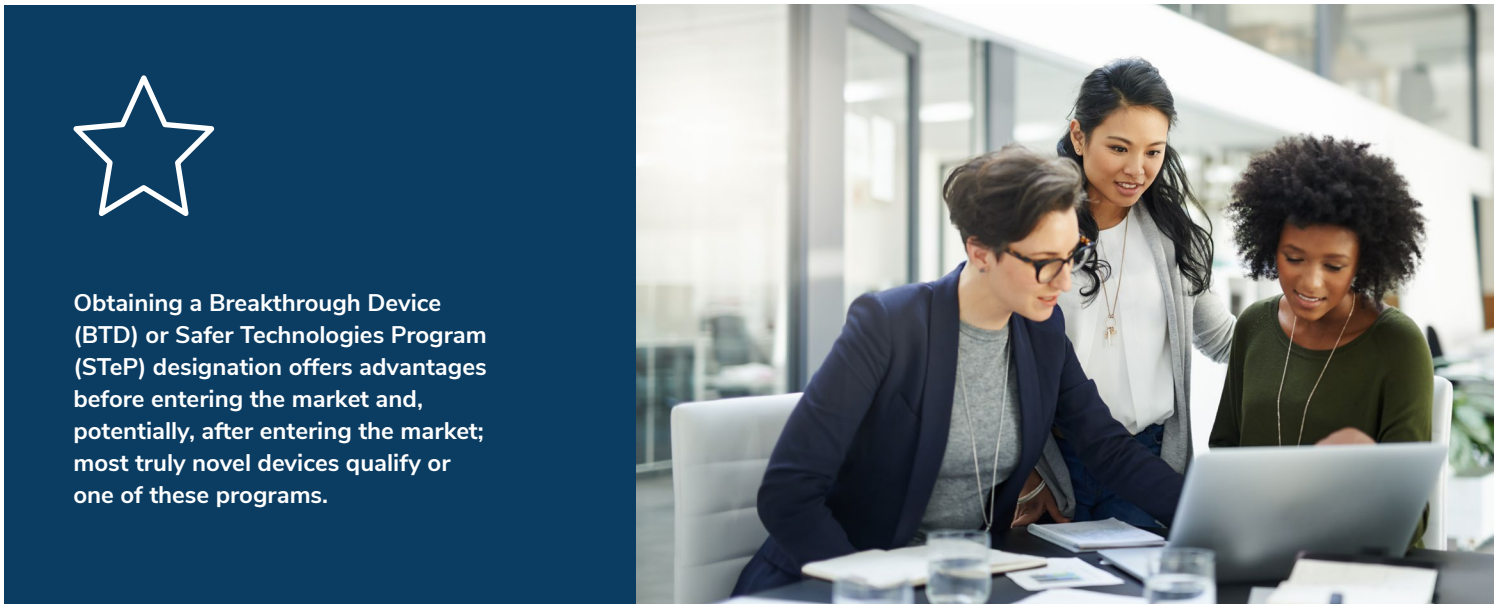
To take full advantage of these programs, a company should submit a request for the appropriate designation as soon as possible. However, the FDA will only grant the designation once there is sufficient evidence to demonstrate the probable advantage, meaning that at least some performance testing needs to be completed first.

Early Payor Feedback Program (EPFP)[16]

Obtaining marketing authorization is a huge and important step for a manufacturer, but they also need to ensure that they will be paid appropriately, which in many cases means through public payors (like Medicare and Medicaid) and/or private payors (insurance). The FDA and payors do not always expect the same data to make their decisions, and sometimes payors have required additional clinical trials, which is expensive for the manufacturer. Additionally, obtaining coverage decisions can be time-consuming.

The Early Payor Feedback Program (EPFP) is intended to address these issues. Essentially, the manufacturer can request that one or more payors be included in a Q-Submission so that the meeting is not only between the manufacturer and FDA, but also includes the appropriate payors. This facilitates discussion between all parties and hopefully allows fewer clinical trials to obtain both marketing authorization from the FDA and coverage decisions from the appropriate payors.

Additionally, parallel review of pivotal clinical trials by the FDA and the Centers for Medicare and Medicaid Services (CMS) is now acceptable, further reducing gaps between FDA marketing authorization and CMS coverage decisions.



Obtaining a Breakthrough Device (BTD) or Safer Technologies Program (STeP) designation offers advantages before entering the market and, potentially, after entering the market; most truly novel devices qualify or one of these programs.

Summary and conclusion

A device that is innovative in terms of design, principles of operation, materials or indications for use presents challenges to the manufacturer. However, the rewards to the manufacturer and to the US public for bringing unique devices to the market often far outweigh those challenges.

Some innovative devices may not be considered truly novel from a regulatory standpoint, meaning that although it is innovative, it is similar enough to devices on the market that there are no new or different questions related to the safety or effectiveness of the device compared to similar devices. Many of these devices can be cleared through a 510(k), although high-risk devices require a PMA. A Pre-Sub is often recommended to ensure alignment with the FDA.

Novel devices present more challenges from a regulatory standpoint, and a Pre-Sub is always recommended to ensure alignment with the FDA.

Manufacturers of novel devices may take advantage of one or more special programs intended to facilitate alignment and expedite market entry for these devices. These programs include the BTD and STeP programs, which offer similar advantages, including enhanced FDA feedback and prioritized review, and EPFP, intended to minimize the time between FDA authorization and insurance coverage decisions. It is recommended to participate in the programs relevant for your device.

Devices that are novel generally are not eligible for clearance through a 510(k). However, there are additional potential pathways to market to consider — specifically, De Novo classification requests for devices that are not high-risk and HDEs for devices that are high-risk and intended for rare diseases or conditions. High-risk novel devices not intended for rare diseases or conditions still require a PMA in most cases. If a novel or innovative device is intended to address an emergency, an EUA may also be an appropriate — but temporary — marketing authorization option.

In conclusion, novel devices often offer great advantages for public health and manufacturers, but also present challenges, especially in achieving alignment with the FDA. A manufacturer should explore options to expedite their device to market and carefully consider their pathway to market.

References

1. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm
2. https://www.fda.gov/combination-products/guidance-regulatory-information
3. https://www.fda.gov/medical-devices/premarket-submissions-selecting-and-preparing-correct-submission/premarket-notification-510k
4. https://www.fda.gov/media/155888/download
5. https://www.fda.gov/media/78456/download
6. www.fda.gov/regulatory-information/search-fda-guidance-documents/how-write-request-designation-rfd
7. https://www.fda.gov/medical-devices/classify-your-medical-device/how-determine-if-your-product-medical-device
8. www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program
9. https://www.fda.gov/medical-devices/premarket-submissions-selecting-and-preparing-correct-submission/de-novo-classification-request
10. www.fda.gov/regulatory-information/search-fda-guidance-documents/humanitarian-device-exemption-hde-program
11. www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization
12. www.fda.gov/medical-devices/premarket-submissions-selecting-and-preparing-correct-submission/investigational-device-exemption-ide
13. www.fda.gov/medical-devices/how-study-and-market-your-device/breakthrough-devices-program
14. www.fda.gov/medical-devices/how-study-and-market-your-device/safer-technologies-program-step-medical-devices
15. www.fda.gov/media/164837/download?attachment
16. www.fda.gov/about-fda/cdrh-innovation/medical-device-coverage-initiatives-connecting-payors-payor-communication-task-force

Learn more

Need help with US FDA compliance? Emergo by UL helps medical technology developers register with the US FDA and in other markets worldwide. Here are some of the ways we can help:

- FDA 510(k) and De Novo submissions
- 21 CFR Part 820 quality management system compliance
- Medical device consulting and training
- Regulatory pathways
- BTD and STeP designations
- 513(g)s and Pre-Submissions

To learn more, visit **EmergobyUL.com/market-access-united-states**.

About the author

Sarah Marie Fitzgerald, RAC (US), is a senior consultant at Emergo by UL. With nearly 20 years of experience in regulatory and quality affairs, Sarah's primary area of expertise is US FDA medical device registrations.

EMERGO
by UL

EmergobyUL.com

PLC23CS1216550